George W Hunter, III, Ph D, Col U S A, (Ret)

Lecturer in Microbiology
College of Medicine and Biological Sciences University College,
University of Florida Gainesville Florida
Formerly Chief Section of Parasitology—Entomology
Fourth Army Area Medical Laboratory
Fort Sam Houston Texas
Professor of Parasitology Affiliated Units of the Graduate School
Baylor University
Chief Department of Medical Zoology
406th Medical General Laboratory Tokyo Japan

William W Frye, Ph D M D, Sc D (Hon)

Professor of Tropical Medicine Dean School of Medicine
and Vice President Louisiana State University New Orleans
Senior Visiting Physician Charity Hospital of Louisiana
Member Commission on Enteric Infections
Armed Forces Epidemiological Board
Formerly Chairman Parasitology and Tropical
Medicine Study Section U S Public Health Service

J Clyde Swartzwelder, Ph D

Professor of Medical Parasitology Louisiana State University
School of Medicine New Orleans Louisiana
Consultant in Parasitology
Veterans Administration Hospital New Orleans
Visiting Scientist Charity Hospital of Louisiana
Formerly Chief (Major AUS) Field Survey Branch
Tropical Disease Control Division
Office of the Surgeon General U S Army

W. B. Saunders Company

Philadelphia 1960 *London*

Third Edition

A Manual of Tropical Medicine

323 illustrations, 8 in color

Made in the United States of America at the press of W B Saunders Company

Library of Congress Catalog Card Number: 60-5421

THE AUTHORS AND COLLABORATORS

OF THE THIRD EDITION OF *A Manual of Tropical Medicine*

WISH TO EXPRESS THEIR TRIBUTE TO

COLONEL THOMAS T MACKIE MC AUS (RETIRED)

FOR HIS CONTRIBUTION IN HELPING TO DEVELOP THIS BOOK

With the global dimensions of World War II came the need for a volume on Tropical Medicine which [illegible] [illegible] serve the Armed Forces and the first edition of the Manual which was designed to fill this need was one of a series of military handbooks sponsored by the National Research Council Colonel Mackie's breadth of experience was a major factor in the success of this Manual This was only one of his many contributions to Tropical Medicine His untimely death made it necessary to seek new co-authors for this third edition We hope that our efforts are in keeping with his ideals



List of Collaborators

R. Tucker Abbott, Ph D.

Pilsbry Chair of Malacology Academy of Natural Sciences of Philadelphia

MOLLUSKS

Victor M Arean, M D.

Associate Professor of Pathology College of Medicine University of Florida Gainesville

CHAGAS' DISEASE

E. J. Bell, Sc.D

Senior Scientist Rocky Mountain Laboratory National Institutes of Health National Microbiological Institute Hamilton Montana

RICKETTSIAL DISEASES (2d ed)

George R Callender, M D.

Brig General M C U S A (Retired)
Director Pathology and Allied Sciences Service, Veterans Administration Member Scientific Advisory Board of the Armed Forces Institute of Pathology, Consultant Gorgas Memorial Institute Consultant Walter Reed Memorial

DIARRHEAL DISEASES (2d ed)

Norman F. Conant, Ph D.

Chairman Department of Microbiology Professor of Mycology Associate Professor of Bacteriology School of Medicine Duke University Consultant to the National Institutes of Health Institute of Allergy and Infectious Diseases Graduate Training Grant Committee

MYCOTIC DISEASES

Gordon E Davis S M , Sc D

Formerly *Principal Medical Bacteriologist Rocky Mountain Laboratory National* Institutes of Health National Microbiological Institute Hamilton Montana Consultant Naval Medical Research Unit No 3 Cairo Egypt

RELAPSING FEVERS

Vincent J. Derbes, M D.

Professor of Medicine Director of Division of Allergy and Dermatology Tulane University School of Medicine New Orleans

FIRE ANTS

Paul D. Ellner, Ph D.

Instructor Department of Microbiology College of Medicine University of Florida Gainesville

BRUCELLOSIS TULAREMIA FOOD POISONING

John P. Fox, Ph D M D , M P H.

Chief Division of Epidemiology Public Health Research Institute of the City of New York, Inc New York

William S. Gochenour, V.M D.

Lt Colonel V C, U S A
Chief, Animal Assessment Branch U S Army Medical Unit, Walter Reed Army Medical Center, Fort Detrick Maryland

LEPTOSPIRAL DISEASES, RAT-BITE FEVERS

Irving Gordon, M.D.

Professor and Chairman Department of Medical Microbiology University of Southern California School of Medicine Los Angeles Senior Attending Physician Los Angeles County General Hospital

VIRUS DISEASES

Robert L. Hullinghorst, M D. (deceased)

Colonel M C U S A
Deputy Commander U S Army Medical Research and Development Command Deputy Special Assistant to The Surgeon General for Research and Development Affairs Washington D C

EPIDEMIC HEMORRHAGIC FEVER

Rodney C. Jung M.D., Ph D.

Associate Professor of Tropical Medicine Tulane University School of Medicine New Orleans

FIRE ANTS

Kenneth L. Knight, Ph D.

Captain M S C U S N
Executive Officer Naval Medical Field Research Laboratory Camp Lejeune N C

ARACHNIDA

Arthur P. Long M D., D P H.

Colonel M C U S A
Chief Preventive Medicine Division Office of The Surgeon General Department of the Army

SMALLPOX (2d ed)

Jean Mayer, Ph D , Sc D.

Associate Professor of Nutrition Harvard University Consultant in Nutrition for Food and Agriculture Organization of the United Nations Consultant in Nutrition Children s Hospital Boston

NUTRITIONAL DISEASES

Henry Edmund Meleney, M.D.

Emeritus Professor of Preventive Medicine College of Medicine New York University Recently [illegible]
University Ne[illegible]
partment Gai[illegible]
of Medicine University of Florida Gainesville

SCHISTOSOMIASIS

Harry Most M.D., D.T.M &H.

Hermann M Biggs Professor of Preventive Medicine, New York University—Bellevue Medical Center Visiting Physician Bellevue Hospital New York City

LEISHMANIASIS

John P. O Brien, M D., M C.P.A.

Post Graduate Lecturer in Pathology, The University of Sydney, Australia, Pathologist Lewisham Hospital Sydney

TROPICAL ULCER DESERT SORE, CUTANEOUS DIPHTHERIA, EFFECTS OF HEAT

Charles S. Petty M.S , M.D.

Assistant Medical Examiner State of Maryland Assistant Professor of Forensic Pathology University of Maryland School of Medicine, Baltimore

TOXICOLOGY OF INSECTICIDES

Cornelius B Philip, Ph.D., Sc.D. (Hon)

Principal Medical Entomologist U S Department of Health, Education and Welfare Public Health Service National Institutes of Health National Institute of Allergy and Infectious Diseases Rocky Mountain Laboratory, Hamilton, Montana

RICKETTSIAL DISEASES

Albert B Sabin M.D.

Professor of Research Pediatrics University of Cincinnati College of Medicine Member Commission on Viral Infections of the Armed Forces Epidemiological Board

VIRUS DISEASES TOXOPLASMOSIS (2nd ed)

Arvey C. Sanders M.S

Lt Colonel MSC USA
Department of Bacteriology Walter Reed Army Institute of Research Washington DC

DIAGNOSIS OF DIARRHEAL DISEASES

Carroll N. Smith, Ph.D.

Head of the Insects Affecting Man Section Insects Affecting Man and Animals Research Branch Entomology Research Division ARS USDA Orlando Florida

MEDICALLY IMPORTANT ARTHROPODS

Frederick J Stare Ph D , M D

Professor and Chairman Department of Nutrition Harvard University Associate in Medicine Peter Bent Brigham Hospital Consultant to Interdepartmental Committee on Nutrition for National Defense

NUTRITIONAL DISEASES

Herbert G Stoenner, D V M

Senior Veterinarian US Department of Health Education and Welfare Public Health Service National Institutes of Health National Institute of Allergy and Infectious Diseases Rocky Mountain Laboratory Hamilton Montana

Q FEVER

Emanuel Suter, M D

Professor and Head Department of Microbiology College of Medicine University of Florida Gainesville

TUBERCULOSIS

ps Thygeson, M.D., Oph.D.

fessor of Ophthalmology, University of California School of Medicine, Director the Francis I Proctor Foundation for Research in Ophthalmology, San Francisco

CHOMA

W. Wade, M.D.

Pathologist Emeritus, Leonard Wood Memorial, Culion Sanitarium, Palawan, Philip pines

LEPROSY

Luther S. West, Ph.D.

Head Department of Biology, Northern Michigan College, Marquette, Michigan Faculty Associate, Rackham School of Graduate Studies, University of Michigan, Consultant, World Health Organization

DIPTERA, MYIASIS

C. Brooke Worth, M.D.

Staff Member, Medical and Natural Sciences, The Rockefeller Foundation

MEDICALLY IMPORTANT ANIMALS

Robert H. Yager, V.M.D.

Colonel, V C , U S A
Assistant to the Commanding Officer, U S Army Medical Unit, Walter Reed A
Medical Center, Fort Detrick, Maryland

LEPTOSPIRAL DISEASES, RAT-BITE FEVERS

Martin D. Young, Sc.D

Scientist Director, Head, Section on Epidemiology, Laboratory of Parasite C therapy, National Institute of Allergy and Infectious Diseases, National Insti Health, Columbia, S C , Member, Expert Panel on Malaria, World Health zation

Preface to the Third Edition

The first edition of the *Manual of Tropical Medicine* was prepared during World War II to meet the need of the Armed Forces in the tropics The concise presentation of essential practical aspects of the more important tropical diseases resulted in acceptance of the *Manual* as a textbook for medical students and for nonmilitary personnel in medicine public health and allied fields

The need for trained personnel in the many disciplines encompassed by tropical medicine has grown with the responsibilities and expanding activities of the United States in the field of international health These activities being carried on in cooperation with many tropical countries are consonant with the desire of the United States to contribute to the improvement of the standards of world health Better health through international cooperation and technical assistance in an attack on disease in the tropics is one of America s finest exports and is symbolic of our country s humanitarian principles

The desire of Americans to visit and learn more about other lands has resulted in the development of international tourism as a major industry The improvement of road systems traversing the Americas will result in an acceleration in travel between the United States and Central and South America Likewise the increased commercial ties between indus tries in the United States and countries in tropical areas necessitate fre quent travel and often residence in warm climates The migration of large population groups from the Carribean to this country, our trustee-ships under the United Nations, technical assistance missions and our

litary defense obligations abroad—all require improved training of
hysicians in the recognition and treatment of tropical and semitropical
iseases. Many medical students of today, through required military
ervice or other governmental duties, will be responsible for the medical
care of overseas military and civilian personnel.

Efforts are being made to improve the teaching of tropical medicine, tropical public health and parasitology. Our present teachers, graduate students, medical students and investigators, through the cooperation of physicians and other scientists in the tropics, are obtaining training and experience with tropical diseases in their natural environment. The present authors hope that the current edition of *A Manual of Tropical Medicine* will contribute to this effort.

As in previous editions of the *Manual*, the primary objective is the concise presentation of the etiology, epidemiology, pathology, clinical characteristics, diagnosis, treatment, control and prophylaxis of the im
portant diseases of the tropics and temperate climates. Since bacterial
parasitic, viral, rickettsial, mycotic and nutritional diseases constitu
significant problems in the practice of medicine, this book is designed
present pertinent information about the major infectious diseases, nu
tional disorders and other conditions. Many of these diseases are
endemic or have their biologic analogs or epidemiologic counterpar
the subtropical and temperate zones as well as in the tropics prope

This third edition has been revised and rewritten extensively to r
the more important recent advances in knowledge of the disease
ered by this book. Tuberculosis is an important health problem in
countries and has been included in this edition, as have also the
viruses, ECHO viruses, visceral larva migrans, alveolar hydatid
kwashiorkor, tropical eosinophilia, interstitial plasma cell pneum
Trypanosoma rangeli. The material on insect control has beer
dated in concise tabular form. The marked increase in the
variety of insecticides for agricultural and public health purp
of which are dangerous if used without adequate safeguards. Th
the inclusion of a chapter on the toxicology of pesticides. The
medical entomology has been reorganized, revised and co
still retains the important epidemiologic information on rel
arthropods and human disease. The chapter on anthelmin
eliminated, and the material on chemotherapy of helminth
ing the recent advances, is incorporated with the discu
disease.

The broad expanse of tropical medicine includes so ma
specialties that, in present times, authoritative presenta
tained by the contributions of many collaborators. Indiv
for exceptional knowledge in specific fields were invite
the revision of certain sections and chapters. The co
collaborator is indicated in the byline of each chapter
heading. If the chapter was prepared originally by
collaborators of the second edition, this is indicated
d by." Chapters with no indicated authorship
sed by the current authors.

Acknowledgments for the Third Edition

e of the third edition make
eferences which have been
listing of such references
would increase the size of this manual to such an extent that the authors would have had to abandon the original concept of a single compact volume of useful and practical information For those who desire to pursue a subject in more detail it is suggested they consult such compendia as the *Current List of Medical Literature Biological Abstracts* and the *Tropical Diseases Bulletin*

As in the other editions materials have been drawn from numerous medical scientific and technical journals recent monographs and abstracting journals such as the *Tropical Diseases Bulletin* without which such a revision would have proved an impossible undertaking

We wish to express once again our deep appreciation to those individuals cited in the first and second editions of *A Manual of Tropical Medicine* and especially to Doctor T T Mackie and Doctor C Brooke Worth two of the original coauthors who contributed so much to the writing of the earlier editions Deep appreciation is due our collaborators who furnished the basic manuscripts for the presentation of subjects in their special spheres of interest In many instances they provided or added original material

Acknowledgments for the Third Edition

...hers including Mr S H Abadie and Doctors D Alessandro Baci... po P C Beaver F S Blanton G J Buddingh H E Discomb... D Ellner J C Geer George E Gifford James V Griffo Jr D J... dry Marshall Hertig R C Jung Harry N March Luis Mazzotti... Miller J H Miller J F Mueller R J Muelling Moselio Schaecter... H Seabury E Suter C J Weinmann and C R Womack advised and ...isted the authors in correlating material in their specialized fields ...ppreciation is extended to those who furnished help and guidance in ...e preparation of the section on Laboratory Diagnostic Methods espe... ...ally to Doctors Marion M Brooke Morris Goldman and Mae Melvin ...f the Communicable Disease Center

Grateful appreciation is also due the Armed Forces Institute of Pathol...ogy for many of the illustrations of Pathology All cuts *not* bearing a special acknowledgment were furnished through the courtesy of this group

The authors wish to express their appreciation to Doctor D B Mc Mullen for his interest and help in securing data for the third edition to Dean G T Harrell for his support and suggestions for the revision of the *Manual* and to Doctor Alan Stone for his work in verifying the species of mosquito vectors

Appreciation is expressed to Mr Robert L Hay and Doctor Robert L Simmons for photographic assistance and to Mr Donald M Alvarado Mr Robert O Beach and Mr John M Hutcheson for the art work which made possible many new figures for this edition

Although it has not proved practicable to include a general bibliogra... phy the following volumes should be mentioned as sources to which readers might go for additional information upon a particular subject This of course does not include the numerous publications and peri... odicals of the Army Navy and United States Public Health Service and... the many journals in tropical medicine and parasitology that are avai... able and are far too numerous to mention here

Adams and Maegraith *Clinical Tropical Diseases* Springfield Ill C... Thomas 1953

Anderson Bostick and Johnstone *Amebiasis* Springfield Ill C... Thomas 1953

Ash and Spitz *Pathology of Tropical Diseases* Philadelphia W... Saunders Co 1945

Belding *Textbook of Clinical Parasitology* 2nd ed New York Apple... Century Crofts 1952

Belding *Basic Clinical Parasitology* New York Appleton Century C... 1958

Boyd *Malariology* 2 vols Philadelphia W B Saunders Co 1949

Brumpt *Précis de Parasitologie* 6th ed Paris Masson et cie 1949

Cameron *Parasites and Parasitism* New York John Wiley & Sons

Chandler *Introduction to Parasitology* 9th ed New York John... & Sons 1955

Conant Smith et al *Manual of Clinical Mycology* 2nd ed P... phia W B Saunders Co 1954

Craig and Faust *Clinical Parasitology*, 6th ed Philadelphia, Lea & Febiger, 1958

Dawson, et al *Report of Proceedings, Third International Congress for Microbiology* New York, International Association of Microbiologists, 1940

Faust *Human Helminthology*, 3rd ed Philadelphia, Lea & Febiger, 1949

Hackett *Malaria in Europe* London, Oxford University Press, 1937

Herms *Medical Entomology*, 4th ed New York, The Macmillan Co, 1956

James A Oliver's and Dudley Jackson's treatises on snakebite in Bercovitz *Clinical Tropical Medicine* New York, Paul B Hoeber, 1944

Lwoff *Biochemistry and physiology of protozoa*, Vols I & II New York, Academic Press Inc, 1951, 1955

Macdonald, G *The epidemiology and control of malaria* London, Oxford University Press, 1957

Manson-Bahr *Manson's Tropical Diseases*, 14th ed Baltimore, Williams & Wilkins Co, 1954

Markell & Voge *Diagnostic Medical Parasitology* Philadelphia, W B Saunders Co, 1958

Moulton, et al *A Symposium on Human Malaria* Washington, American Association for the Advancement of Science, 1941

Moulton, et al *A Symposium on Relapsing Fever in the Americas* Washington, American Association for the Advancement of Science, 1942

Napier *The Principles and Practice of Tropical Medicine*, 2 vols New York, The Macmillan Co, 1946

Preventive Medicine in World War II, Vol IV Communicable Diseases Medical Department, United States Army Edited by J B Coates, Jr, Col MC, E C Hoff and P M Hoff U S Government Printing Office, 1958

Riley and Johannsen *Medical Entomology*, 2nd ed New York, McGraw-Hill Book Co, 1938

Russell, West and Manwell *Practical Malariology* Philadelphia, W B Saunders Co, 1946

Sawyer, W A, et al *Proceedings of the Fourth International Congresses of Tropical Medicine and Malaria* U S Government Printing Office, 1948

Shattuck *Diseases of the Tropics* New York, Appleton Century Crofts, 1949

Simmons, et al *Global Epidemiology* Philadelphia, J B Lippincott Co, Vol I, 1945, Vol II, 1951, Vol III, 1954

Simmons and Gentzkow *Laboratory Methods of the United States Army*, 5th ed Philadelphia, Lea & Febiger, 1944

Strong *Stitt's Diagnosis, Prevention and Treatment of Tropical Diseases*, 2 vols, 7th ed Philadelphia, Blakiston Co, 1944

Trussell *Trichomonas vaginalis and Trichomoniasis* Springfield, Ill, C C Thomas, 1947

Wenyon *Protozoology*, 2 vols New York, William Wood & Co 1926

Special appreciation and gratitude are due Mrs Adelaide W Hunter

Acknowledgments for the Third Edition

thers including Mr S H Abadie and Doctors D Alessandro Baci
upo P C Beaver F S Blanton G J Buddingh H E Dascomb
al D Ellner J C Geer George E Gifford James V Griffo Jr D J
ıdry Marshall Hertig R C Jung Harry N March Luis Mazzotti
Miller J H Miller J F Mueller R J Muelling Moselio Schaecter
H Seabury E Suter C J Weinmann and C R Womack advised and
sisted the authors in correlating material in their specialized fields
ppreciation is extended to those who furnished help and guidance in
he preparation of the section on Laboratory Diagnostic Methods espe
ıally to Doctors Marion M Brooke Morris Goldman and Mae Melvin
of the Communicable Disease Center

Grateful appreciation is also due the Armed Forces Institute of Pathol
ogy for many of the illustrations of Pathology All cuts *not* bearing a
special acknowledgment were furnished through the courtesy of this
group

The authors wish to express their appreciation to Doctor D B Mc
Mullen for his interest and help in securing data for the third edition
to Dean G T Harrell for his support and suggestions for the revision
of the *Manual* and to Doctor Alan Stone for his work in verifying the
species of mosquito vectors

Appreciation is expressed to Mr Robert L Hay and Doctor Robert
L Simmons for photographic assistance and to Mr Donald M Alvarado
Mr Robert O Beach and Mr John M Hutcheson for the art work which
made possible many new figures for this edition

Although it has not proved practicable to include a general bibliogra
phy the following volumes should be mentioned as sources to whic
readers might go for additional information upon a particular subjec
This of course does not include the numerous publications and pe
odicals of the Army Navy and United States Public Health Service a
the many journals in tropical medicine and parasitology that are a
able and are far too numerous to mention here

Adams and Maegraith *Clinical Tropical Diseases* Springfield Ill C
Thomas 1953
Anderson Bostick and Johnstone *Amebiasis* Springfield Ill C
Thomas 1953
Ash and Spitz *Pathology of Tropical Diseases* Philadelphia W
Saunders Co 1945
Belding *Textbook of Clinical Parasitology* 2nd ed New York App
Century Crofts 1952
Belding *Basic Clinical Parasitology* New York Appleton Century
1958
Boyd *Malariology* 2 vols Philadelphia W B Saunders Co 19
Brumpt *Precis de Parasitologie* 6th ed Paris Masson et cie 19
Cameron *Parasites and Parasitism* New York John Wiley & Sor
Chandler *Introduction to Parasitology* 9th ed New York Joh
& Sons 1955
Conant Smith et al *Manual of Clinical Mycology* 2nd ed
phia W B Saunders Co 1954

Craig and Faust *Clinical Parasitology*, 6th ed Philadelphia, Lea & Febiger, 1958
Dawson et al *Report of Proceedings, Third International Congress for Microbiology* New York, International Association of Microbiologists 1940
Faust *Human Helminthology*, 3rd ed Philadelphia Lea & Febiger, 1949
Hackett *Malaria in Europe* London, Oxford University Press, 1937
Herms *Medical Entomology*, 4th ed New York, The Macmillan Co, 1956
James A Oliver s and Dudley Jackson s treatises on snakebite in Bercovitz *Clinical Tropical Medicine* New York, Paul B Hoeber, 1944
Lwoff *Biochemistry and physiology of protozoa*, Vols I & II New York, Academic Press, Inc, 1951, 1955
Macdonald, G *The epidemiology and control of malaria* London, Oxford University Press, 1957
Manson Bahr *Manson s Tropical Diseases*, 14th ed Baltimore, Williams & Wilkins Co, 1954
Markell & Voge *Diagnostic Medical Parasitology* Philadelphia, W B Saunders Co, 1958
Moulton et al *A Symposium on Human Malaria* Washington, American Association for the Advancement of Science, 1941
Moulton, et al *A Symposium on Relapsing Fever in the Americas* Washington, American Association for the Advancement of Science, 1942
Napier *The Principles and Practice of Tropical Medicine*, 2 vols New York The Macmillan Co, 1946
Preventive Medicine in World War II, Vol IV Communicable Diseases Medical Department, United States Army Edited by J B Coates, Jr, Col MC, E C Hoff and P M Hoff U S Government Printing Office, 1958
Riley and Johannsen *Medical Entomology*, 2nd ed New York, McGraw-Hill Book Co, 1938
Russell, West and Manwell *Practical Malariology* Philadelphia, W B Saunders Co, 1946
Sawyer W A, et al *Proceedings of the Fourth International Congresses of Tropical Medicine and Malaria* U S Government Printing Office, 1948
Shattuck *Diseases of the Tropics* New York, Appleton-Century Crofts, 1949
Simmons, et al *Global Epidemiology* Philadelphia, J B Lippincott Co, Vol I 1945, Vol II, 1951, Vol III, 1954
Simmons and Gentzkow *Laboratory Methods of the United States Army*, 5th ed Philadelphia, Lea & Febiger, 1944
Strong *Stitt s Diagnosis, Prevention and Treatment of Tropical Diseases*, 2 vols, 7th ed Philadelphia Blakiston Co, 1944
Trussell *Trichomonas vaginalis and Trichomoniasis* Springfield, Ill, C C Thomas, 1947
Wenyon *Protozoology*, 2 vols New York, William Wood & Co, 1926

Special appreciation and gratitude are due Mrs Adelaide W Hunter

for reading the entire galley and page proof Likewise our sincere thanks are extended to Miss Margarette Bahm Miss Kate Minor Olivier and Mrs Dorothy S Sappington for their aid in the preparation of the typescript

Finally the authors wish once again to express their deep appreciation to the publishers W B Saunders Company, for their interest and invaluable assistance which made this third edition possible

THE AUTHORS

Contents

I Virus Diseases

VIII Nutritional Diseases

IX Miscellaneous Conditions

X · Medically Important Mollusks

XI · Medically Important Arthropods

XII Some Laboratory Diagnostic Methods

I

Virus Diseases

1

Introduction

Irving Gordon

Viruses are small infectious entities that are reproduced only in susceptible living cells. The metabolism of a susceptible cell that has been penetrated by an infectious virus particle is diverted by virus nucleic acid or nucleoprotein to a new biosynthetic pathway. The result is formation of new virus. The rate of production of new virus may be high or low, damage to tissues may be rapid or slow, and the outcome of the viral infection may vary from no effect to necrosis, proliferation or neoplastic change. Sometimes viruses cause latent infections. Such infections persist in tissues for long periods, often without accompanying morphologic changes. The latently infected host, however, frequently develops antibody.

The unique nature of virus multiplication makes it difficult to find substances that selectively interfere with virus synthesis without also interfering with normal cellular metabolism, and at present there are no specific chemotherapeutic agents or antibiotics that are effective against viruses and practicable for treatment of infected patients. The agents that cause psittacosis, lymphogranuloma venereum and trachoma are considered to belong to a borderline group. They resemble rickettsiae as much or more than they resemble viruses. In contrast to the true virus infections, diseases caused by agents of this borderline group can be treated effectively with certain antibiotics and chemotherapeutic agents that are also effective against bacteria.

The host range of most viruses and the range of susceptible tissues are relatively broad. Classification schemes that are based on the predilection

of a virus to involve selected hosts, tissues or systems of the body may not reflect [illegible] een viruses For example, so called [illegible] 's can grow in arthropod and bird [illegible] In spite of the name "encephalitis viruses," they often cause systemic disease without neurologic involvement in man Some are closely related biologically, immunologically and morphologically to other arthropod-borne viruses, such as yellow fever or dengue The latter cause diseases that are clinically quite different from typical encephalitis and that are distinct from one another Such biologic and immunologic similarities are of importance not only in clinical diagnosis, but also in the interpretation of laboratory tests and in the recognition of epidemiologic patterns helpful in prevention and control An informal scheme of grouping the viruses is presented here that takes into account their interrelationships

Virus Groups

The criteria used to group viruses include the physical and chemical properties of the virus particle, the characteristics of viral multiplication in susceptible cells, including cytologic and histopathologic distinctions, and antigenic relationships In viral as in bacterial infection, the nature and amount of cellular damage or change, and consequently the pathogenesis of disease, depend upon such factors as the virulence of the virus and the nature of the host response, including immune responses When viruses mutate, such characteristics as their virulence and antigenicity may be altered independently of one another. Furthermore, if a single cell happens to become doubly or multiply infected with virus particles which differ both in virulence and antigenicity, components of the two particles sometimes recombine during the multiplication process This may result, like mutation, in the emergence of variants with increased or decreased virulence or changed antigenic properties.

Accordingly, there is marked variation in the pathogenesis severity, symptoms, frequency and distribution of diseases caused by different members of the same virus group Smallpox and vaccinia viruses provide well known examples They are both members of the same group (the so called poxviruses) For man, smallpox virus is virulent, vaccinia virus relatively avirulent The two are closely related antigenically, however, so that, as everyone knows, vaccination with vaccinia virus effectively immunizes against smallpox

In some virus groups the converse situation may occur Antigenic variants of a given virus can have almost the same degree of virulence Each of the antigenic variants may consequently induce clinically uniform but epidemiologically distinct disease, infection with one variant evokes antibodies that are ineffective in protecting the same population against subsequent infection with an antigenically different variant An example is the influenza viruses Consecutive infection with influenza viruses A and B respectively is common Symptoms and signs exhibited by patients are generally much the same in the two diseases

Table I 1 lists some viruses by groups and gives a tabulation of common clinical manifestations of diseases caused by their respective agents

Most of the viruses mentioned induce domestic as well as tropical diseases The arthropod borne viruses are discussed in Chapter 2, and certain ungrouped viruses in Chapter 4 Additional comments concerning the characteristics of the several virus groups and the diseases caused by their members follow

Table 1.1. Symptoms* of Some Human Virus Infections, by Virus Groups**

SOME VIRUSES BELONGING TO WELL DEFINED GROUPS	SOME MANIFESTATIONS OF HUMAN INFECTION									
	RESPIRATORY		GASTRO INTESTINAL		CNS		SKIN MUCOUS MEMBRANES AND GENITOURINARY TRACT			
	MOUTH OR PHARYNX	BRONCHI OR LUNGS	VIRUS IN FECES	DIARRHEA	ASEPTIC MENINGITIS	RESIDUAL PARALYSIS	MACULOPAPULAR OR PETECHIAL RASH	VESICULAR OR PUSTULAR RASH	PRIMARY EYE INFECTION	GENITOURINARY INFECTION
Psittacosis—LGV										
Psittacosis		C			R		O			
Lymphogranuloma venereum			R						R	C
Trachoma									C	
Poxviruses										
Smallpox	C	C						C	R	
Herpes viruses										
Herpes simplex	C				O	R		C	C	O
Herpes zoster & varicella	C	O			O	O		C	C	O
Adenoviruses										
Types 1–18	C	C	C						C	
Myxoviruses										
Influenza viruses A & B	C	C								
Mumps virus	C				C	R				C
Hemadsorption I & II										
croup-associated	C	C								
Enteroviruses										
Polioviruses										
Types 1, 2 3	C		C	O	C	C				
Coxsackie viruses										
Group A (25 types)†	C		C	O	C	R		O		
Group B (5 types)			C							
ECHO viruses										
24 types†	C	O	C	C	C	R	C			

* Symptoms are coded with respect to frequency as follows
C = commonly O = occasionally R = rarely

** Arthropod borne infections are not listed nor are syndromes caused by ungrouped viruses

† Not all types cause human disease

The *psittacosis lymphogranuloma venereum* group includes in addition to the agents giving the group its name the agents that cause trachoma and inclusion blennorrhea As previously noted this group of agents is considered to be intermediate between rickettsiae and true viruses and their size reflects this They have an average diameter of 300 mμ or more and are readily visible through the light microscope when they are stained Antigenic relationships between members of the group are of importance in evaluating serologic tests All of these agents progress through developmental stages in the cell each of which is characterized by formation of a distinctive inclusion body At a given stage inclusions due to one agent may resemble those of another although usually there are differences The agents in this group are sensitive to antibiotics particularly the tetracyclines and chloramphenicol

The *poxvirus* group includes smallpox and vaccinia viruses as well as the viruses of molluscum contagiosum and a number of animal diseases The poxviruses are relatively large (230 to 300 mμ) and form intracytoplasmic inclusions consisting of viruses in various stages of development In some but not all respects they resemble inclusions formed by agents of the psittacosis lymphogranuloma venereum group In general poxviruses agglutinate erythrocytes by means of bound lipid Certain members of the group share antigens with one another Like the rest of the viruses they are not susceptible to antibiotics

The *herpes viruses* include the viruses of herpes simplex and of chickenpox as well as those that cause a number of animal infections such as B virus of monkeys The latter can be transmitted to humans by bite Chickenpox virus is probably identical with the virus of herpes zoster Herpes viruses are approximately 135 mμ in diameter They induce characteristic intranuclear inclusions A high degree of latency is typical of the group silent infection often persists in the presence of antibody and causes repeated clinical episodes

The *adenoviruses* are also fairly large (100 mμ) and also form intra

viruses frequently cause latent infections certain adenoviruses frequently can be demonstrated in tonsils of asymptomatic children In the populations studied most children had experienced several adenovirus infections by the age of six years Adenoviruses characteristically

times found in feces it is thought that they do not infect the intestine but instead are swallowed and pass through the gastrointestinal tract without being destroyed

The *myxoviruses* include the viruses of influenza types A, B and C mumps virus and four recently characterized viruses that cause upper respiratory disease or pneumonitis (Sendai virus croup associated virus

and hemadsorption viruses I and II) There are also several viruses of animals that belong to the myxovirus group Their importance in human disease is still being studied The members of the group vary in size between 80 and 150 mμ They agglutinate erythrocytes by linking them through attachment of a specific viral enzyme (sialidase or neuraminidase) to substrate on the red blood cells, they have a predilection for the respiratory tract Myxoviruses are antigenically quite distinct from one another but sometimes possess common antigens, there may be marked antigenic variation among strains within a given type, e g , influenza virus type A2 (Asian strain) is antigenically quite different from A1 or A strains

[illegible] the intestine [illegible] enteroviruses [illegible] manifested by many distinct syndromes The polioviruses, Coxsackie viruses, and so-called "ECHO" viruses all belong to the enterovirus group They are [illegible]

[illegible]

in the pathogenesis of disease, particularly of the central nervous system infection in poliomyelitis

[illegible]

Coxsackie [illegible] types), a[illegible] epidemic [illegible] carditis The ECHO viruses cause respiratory, diarrheal, exanthematous and neurologic syndromes, particularly aseptic meningitis Enteroviruses, particularly ECHO viruses, are also frequent causes of clinically undifferentiated febrile illnesses

[illegible] of [illegible] hr[illegible] etc [illegible] chemical properties but also by antigenic [illegible]

of the arboviruses A large number of these as yet have not been in-
criminated as causes of human disease

There are antigenic relationships between members of a given arbor
virus group (e g Japanese B encephalitis and yellow fever viruses) and
this is important in diagnosis and control Experience with one of the
two viruses is reflected in the status of the immunity in the patient with
respect to the other It has already been pointed out that such relation
ships are significant in the interpretation of serologic tests whether used
as epidemiologic survey tools or as aids in diagnosis and may lead to the
development of vaccination procedures that confer broadened protection

Viruses that are as yet ungrouped include those causing measles,
rabies lymphocytic choriomeningitis and so called salivary gland disease
All have been cultivated and studied in the laboratory There is strong
evidence that infectious hepatitis serum hepatitis infectious mononucle-
osis hemorrhagic fever rubella the common cold and certain forms of
gastroenteritis are caused by viruses but the evidence is derived largely
from experiments in volunteers The respective causative viruses have
not yet been isolated and characterized and laboratory study of thes
agents is at present not feasible

Laboratory Aids in the Diagnosis of Viral Infection

The single most important procedure employed in the diagnosi
viral infection is the *collection of the specimens to be examined* This
termines whether subsequent procedures will be of any value

There are three principal kinds of laboratory examination usef
aids in diagnosis of viral infections The first is the recognition of a
racteristic cytologic or histologic lesion for example the identific
Negri bodies the characteristic inclusion body of rabies Secon
virus may be isolated from the patient's blood secretions or exc
or from tissue (p 827) Third the formation of antibodies may
onstrated shortly following the undiagnosed clinical episode (

To make sure that the clinical syndrome under consideration
time relationship to the antibody response bears a diagnosticall
ally necessary to obtain two or more specimens of serum The
men should be obtained as soon after the onset of illness a
before circulating antibodies have appeared The subsequen
should be collected after circulating antibody levels have rise
of the antigenic stimulation due to infection Usually th
weeks to a month after the onset of illness (p 829)

It is clear that the optimum time for obtaining specimens
study by any of the three general approaches mentioned
siderably in different viral diseases In the section to follov
tion will be made in most cases of the optimum time a
specimens should be taken Table 1 2 summarizes these p
of the standard procedures are outlined in Section VII

In a great many viral infections inapparent infectio
symptoms or signs is commonplace and may eve
...irus might be isolated for example from
... yet the patient's illness migh

Table 1.2 Relationship between the Stage of Illness and the Presence of Demonstrable Virus or Antibody in the Patient*

STAGE OF ILLNESS	VIRUS DEMONSTRABLE IN TEST MATERIAL	SPECIFIC ANTIBODY PRESENT IN SERUM
Incubation period	Rarely	
Prodromal period	Rarely	
Onset	Frequently	
Acute phase	Frequently	Frequently**
Recovery phase	Rarely	Generally
Convalescent phase	Very rarely	Usually

* Adapted from Lennette E H Chapter I of Diagnostic Procedures for Virus and Rickettsial Diseases 2nd Ed American Public Health Assn New York 1956

** Antibody may be present as a result of prior experience with the virus through infection or vaccination (e g influenza) or antibody formation to the infecting virus may be well under way by the time the acute phase blood is taken (e g neutralizing antibody in poliomyelitis and Western equine encephalitis)

cause It is highly desirable therefore to search for a rise in titer of the antibody each time an attempt is made to isolate and identify a virus from clinical material

The complement fixation test is the serologic procedure most frequently

Viruses may be demonstrated by testing the contents of vesicles or crusts for specific complement fixing antigen Microscopic examination of conjunctival scraping obtained from patients with tentative diagnoses of trachoma or inclusion blennorrhea and microscopic examination of the contents of nodules in suspected molluscum contagiosum can provide immediate confirmation of the clinical diagnosis

Immunofluorescence is not routinely available but offers great promise for rapid and accurate diagnosis of some viral infections Antibody labeled with fluorescein or some other fluorescent material is allowed to

While recovery of virus from clinical material is usually too laborious and unrewarding for routine diagnostic purposes it sometimes is a method of choice For example in some of the diseases caused by the arthropod borne viruses the fastest way to identify the causative agents may be to inoculate mice with blood obtained soon after the onset of illness If the patient suffers viremia the inoculated mice often die in two or three days Their tissues can then be used as antigen in a complement fixation test and sometimes the virus can be identified rapidly Furthermore the first cases in a developing epidemic of arthropod borne encephalitis may be fatal and the most rapid way to identify the respon

ble virus can be inoculation of mice with brain tissue obtained at ecropsy (p 827)

It is therefore important to obtain specimens free of bacterial or other contamination and the virus must be preserved by keeping the speci mens cold during storage or shipment It is best to quick freeze specimens at the temperature of frozen carbon dioxide (dry ice) Slow freezing or freezing in ordinary food or refrigerator units is unsatisfactory and some times results in loss of virus Glycerol (50 per cent) helps to preserve many viruses particularly in tissue blocks but these should not be mixed with body fluids Glycerolated specimens should be refrigerated It is advisable to consult with the laboratory if there is any doubt about the proper handling of these specimens

2

Diseases Caused by the Arthropod-borne Viruses

Irving Gordon

Introduction

The name "arthropod borne viruses" describes the single mo tant link between the numerous members of this group tr from vertebrate to vertebrate via an arthropod vector The a borne viruses are generally capable of multiplying in the vect killing it, and the infections they cause are usually transmitted The vector acquires the virus while feeding on an infected undergoing the stages of viremia For some days thereafter extrinsic incubation period the vector is incapable of trar disease Following this it is able to infect new vertebrate ho The ecologic relationships between vector and host and th of the infection in each thus determine the frequency and these diseases

The viruses themselves fall into several groups (Table possess o y contain common antigens

tic physical and chemical properties There are subgroups in group B as indicated in Table I 3 It has been postulated that the differences be tween members of a given class may have evolved due to ecologic and environmental selection pressures so that the several members may have stemmed from common or related ancestors In spite of the close anti genic relationship between members of a given group there can be a wide disparity in the pathogenesis and clinical characteristics of the dis eases caused by antigenically related viruses or even by different strains

Distribution Table I 3 shows that diseases caused by the arthro pod borne viruses are worldwide in distribution They are particularly prevalent in tropical rain forest areas but are also found in irrigated dry places where high concentrations of mosquito vectors occur at times The geographic distribution of the several individual diseases may be quite circumscribed

Etiology The arthropod borne viruses are small ranging from 30 to 50 mμ in diameter The viruses of a given serologic subgroup tend to be of similar size The arthropod borne viruses are unstable at ordinary spring and summer ambient temperatures in temperate zones and are in activated rapidly at tropical temperatures They are also inactivated by sodium desoxycholate, a property which differentiates them from the en teroviruses

Although the arthropod borne viruses as a group are capable of in fecting a wide variety of vertebrate hosts there are great individual differences in the host ranges and also in the character of the infections they induce in animals Some animals develop inapparent infection with viremia thus serving as a reservoir whereas the infection in others may

highly suc cultures have been f effects following infectu

As has already been mentioned the antigenic cross reactions between various members of the different arthropod borne viruses are of im portance not only in classification but also in diagnosis and prevention Demonstration of antibody against a given virus does not necessarily imply that the animal was infected with that virus the infection might have been due to an antigenically related virus By the same token in fection with one virus sometimes confers protection against other viruses in the same group The degree of protection varies with the closeness of the antigenic relationship between the two viruses Finally cross anti genicity is important in vaccination previous experience with an antigen

e I.3. Some Arthropod Borne Viruses that Cause Disease in Man Listed by Groups and Subgroups

VIRUS		PRINCIPAL CLINICAL MANIFESTATIONS					VECTOR	DISTRIBUTION
		SYSTEMIC*						
GROUP	NAME	FEBRILE SYNDROME	FEVER RASH LYMPHADENOPATHY JOINT PAINS	HEMORRHAGIC FEVER	HEPATITIS	ENCEPHALITIC		
A	EEE[1]	x				x	Mosquito	Eastern North & South America Caribbean Central America Philippines
	WEE[2]	x				x	Mosquito	Western North America Argentina
	VEE[3]	x				x	Mosquito	South America Caribbean
	Chikungunya		x		?		Mosquito	East and South Africa
	Mayaro	x						South America Caribbean
B	*Dengue* Type 1	x	x				Mosquito	Eastern and Southern coastal Asia Southwest Pacific Hawaii India New Guinea Trinidad Uganda Philippines Thailand
	Type 2	x	x	x	?			
	Type 3	x		x				
	Type 4	x						
	St Louis encephalitis	x				x	Mosquito	United States Trinidad
	Japanese B encephalitis	x				x	Mosquito	India East Asia Southwest Pacific
	Murray Valley encephalitis	x				x	Mosquito	Australia New Guinea
	West Nile encephalitis	x	x			?	Mosquito	North and Central Africa Middle East India

Table 1.3. Some Arthropod Borne Viruses that Cause Disease in Man, Listed by Groups and Subgroups (*continued*)

GROUP	VIRUS NAME	PRINCIPAL CLINICAL MANIFESTATIONS: SYSTEMIC*: FEBRILE SYNDROME	SYSTEMIC*: FEVER RASH LYMPHADENOPATHY JOINT PAINS	SYSTEMIC*: HEMORRHAGIC FEVER	SYSTEMIC*: HEPATITIS	ENCEPHALITIC	VECTOR	DISTRIBUTION
	Russian tick borne complex						Tick	
	RSSE[4]							USSR
	Omsk hemorrhagic fever	x		x	x	x		USSR
	Central European encephalitis	x				x		Eastern Europe and the Balkans
	Kyasanur Forest			x				India
	Louping ill	x				x		British Isles Eastern Europe
	Yellow fever	x			x		Mosquito	Tropical Africa and America
	Zika	x					Mosquito	Central Africa
	Wesselbron	x					Mosquito	South Africa
C	Marituba	x					Mosquito	Brazil
	Oriboca	x					Mosquito	Brazil
Other	Rift Valley fever	x					Mosquito	Central and South Africa
	Sandfly fever	x					*Phlebotomus*	Mediterranean Black Sea coasts Middle East India

* Under systemic are listed the nonencephalitic syndromes caused by the arthropod borne viruses which may range from trivial to severe febrile syndromes including influenza like illnesses dengue like disease characterized by rash joint pains and lymph node enlargement and the others noted

[1] EEE = Eastern equine encephalitis
[2] WEE = Western equine encephalitis
[3] VEE = Venezuelan equine encephalitis
[4] RSSE = Russian spring-summer encephalitis

followed by injection of vaccine made from an antigenically related virus of the same group results in the anamnestic type of antibody response Resistance to infection correlates well with the amount of circulating antibody

Epidemiology Man is only an incidental host of the arthropod borne encephalitis viruses and probably plays a negligible part in the natural history of the infection cycle that maintains the viruses in nature In some areas identification of the ultimate reservoir of the viruses is still unknown It must be pointed out that vectors known to be capable of contracting an infection with a given arthropod borne virus may not feed upon a vertebrate host with viremia The presence of competent vectors need not necessarily imply the existence of a reservoir of the virus in a given area

The extrinsic incubation period of the arthropod borne viruses in ar thropods is related to temperature the higher the temperature the shorter the extrinsic incubation period This fact can help determine the seasonal patterns since it accelerates or retards the infection cycle The Russian tick borne disease complex often occurs in one spring and sum mer whereas Japanese B encephalitis is an autumnal disease and yello fever and dengue are summer diseases

When a disease such as yellow fever which is normally tropical is troduced into a temperate area frost will eventually kill the mosqu and thus stop transmission Actual eradication of the disease occurs wh there is no winter reservoir The tick borne viruses can be transm from tick to tick by the transovarian route and in such instances th acts both as the vector and as a true reservoir of the virus Mosqu however apparently do not transmit arthropod borne viruses tran ally and so serve only as vectors

There are a number of arthropod borne viruses not listed in T that have been found on the basis of serologic surveys of popul the habitat of the vector to infect man These viruses have not covered from patients exhibiting definable illness and for the pre be excluded when considering a differential diagnosis

Pathology The arthropod borne viruses are usually intro tradermally or subcutaneously and are spread quickly to dista the body owing to the viremia that develops soon afterw agents are capable of multiplying in a wide variety of tissu are often diphasic with a period of invasion followed by pa plete remission and then by major systemic involvement volvement in other instances may merge with the febrile o is not clear how virus goes from the blood to the brain or sp it has been shown experimentally that central nervous s ment does not occur until a threshold concentration of vir is reached Genetic traits have also been shown that de the resistance of a given strain of animal to a given conce in the blood

When encephalitis occurs lesions in the brain are wi lfferentiating these infections from poliomye mporal and occipital portions of th layers of the cerebellum

Otherwise however neuronal lesions and inflammatory reactions due to arthropod borne viru There is perivascular cuffing, e patchy areas of complete n neurono

pathology of the hemorrhagic fever syndrome produced by the arthro pod borne viruses

Clinical Characteristics In general the incubation period of the arthropod borne virus infections is short For example the incubation periods of the 22 cases of yellow fever induced in volunteers by Walter Reed and his associates ranged between three and six days At the ex treme it has been estimated that incubation periods in yellow fever are sometimes as long as three weeks

It should be emphasized once again that a large proportion of the ar thropod borne virus infections are inapparent or clinically undetected However lasting immunity may result from such infections

The pathogenesis of these infections consists of an invasive viremic phase accompanied by influenza like constitutional symptoms and signs followed in some cases by a phase of systemic involvement The two phases are sometimes separated by a few days of partial or complete re mission Onset is likely to be sudden Headache fever or feverishness chills or chilliness malaise weakness photophobia anorexia nausea and sometimes vomiting are common Sore throat, mild conjunctivitis and muscle or joint aches may also be of the type found in influenza

When localizing signs and symptoms develop the pattern of the en suing disease may be dengue like may consist of the hemorrhagic fever syndrome may involve the liver or may be encephalitic The clinical features of classic dengue and of discussed later in the section on disease in which hepatitis is a pr arately

The onset of the encephalitic syndrome may be slow or rapid Convul sions are usual in children but are less frequent in adults Meningeal in volvement is often prominent When present it gives rise to the usual physical signs and cerebrospinal fluid changes Tremors spasticity and paresis or paralysis are common The latter may be of the upper motor neuron type Changes in sensorium are often marked and lethargy drowsiness or coma are so characteristic that these infections were once termed "sleeping sickness" Speech disturbances disorientati n or psy chotic manifestations may accompany the other signs Reflexes are often abnormal but are variable

The course may be brief or prolonged There can be severe weight loss Usually the patient improves greatly when his temperature returns to normal often with in two weeks The incidence of sequelae varies with the causative virus and also with the age of the patient. Sequelae are

more frequent and more severe following infections in infants or children than in adults Even when permanent sequelae do not occur convales cence may be prolonged and improvement slow

There is a sharp marked increase in blood polymorphonuclear leuko cytes early in the disease which is diagnostically suggestive If a cerebro spinal fluid specimen is obtained early in the disease polymorphonuclear leukocytes may be present as in poliomyelitis but these are soon re placed by lymphocytes The degree of pleocytosis does not necessarily reflect the seriousness of the illness The frequency with which the asep tic meningitis syndrome occurs as the chief clinical feature of arthropod borne viral encephalitis has not been accurately ascertained

Diagnosis From a clinical point of view differentiation between the individual diseases in this group is not as important as the identifica tion of the illness in the general category of arthropod borne virus dis cases It is particularly important to suspect that an undifferentiated febrile illness with or without joint pains rash or neurologic manifesta tions might be caused by an arthropod borne virus Diseases to be dif ferentiated from arthropod borne encephalitis include poliomyelitis spo radic infections of the central nervous system such as mumps herpes o rabies and the postinfection encephalitides such as measles or varicell encephalitis

Appropriate specimens should be taken for laboratory confirmation the clinical diagnosis The general principles governing choice method of collection of specimens are given in Chapter I and more cific instructions in Section XII If practical specific instructions sh be obtained from the nearest laboratory capable of carrying out diagnostic tests In any event blood specimens from both the acute convalescent phase should be aseptically collected Since in the phase the blood often contains the virus due precautions should served to prevent autoinfection Serum should be removed from t and specimens should be refrigerated Specimens of brain an should be secured in accordance with instructions (pp 827-828

Whenever a case of arthropod borne infection is suspected an should be made to identify other cases and a search made for t brate reservoir and arthropod vector Inclusion of one of the a borne diseases in a clinical differential diagnosis should alw an appropriate epidemiologic investigation if evidence to s diagnosis is found

Prophylaxis. Live attenuated yellow fever vaccine fective in providing protection against the disease A live also been developed for prevention of dengue viruses types this is not yet commercially available Formalinized vaccine against some of the arthropod borne encephalitides no western and Venezuelan equine encephalitis Vaccin widely used to prevent these infections in horses and m tect persons who are exposed as an occupational hazard immunization is not recommended Experimentally the sed to prevent Japanese B encephalitis and R se of vaccine to halt or ameliorate s too long for immunity t

protection by administration of specific antibody is theoretically possible but has not been put to a practical test

Vector control has played an historic part in the prevention of yellow fever the urban type having been eradicated by this means In irrigated dry areas mosquito control is effective in preventing the spread of arthropod borne encephalitis viruses However in most tropical rain forests mosquito control is out of the question and it is noteworthy that jungle yellow fever continues to spread northward through Central America Tick control is said to be effective against spread of viruses of the Russian tick borne complex

Dengue

Albert B Sabin Revised by Irving Gordon

Synonyms Dandy fever breakbone fever bouquet Philippine

The classic type is a self

in in various parts of the

body prostration rash lymphadenopathy and leukopenia It is transmitted by certain species of mosquitoes belonging to the genus *Aedes* Recently widespread epidemics of hemorrhagic fever have been identified as a second clinical type

Distribution. In considering the distribution of dengue virus in the world one must differentiate between the endemic areas in which the virus is presumably constantly present areas in which strangers and newcomers risk acquiring the infection and areas in which some of the largest epidemics have occurred through importation of the virus but in which experience has shown the disease is not endemic and does not constitute a danger to newcomers Recent experience suggests that certain regions of the Southwest Pacific Northern Australia New Guinea Indonesia India and countries bordering on the South China Sea may be considered to be endemic areas It is also probable that some of the countries and islands in the Western hemisphere in the region of 10° North or South latitude may also constitute endemic areas The information about the incidence of dengue in Africa is sketchy and inadequate It is known that during World War II no confirmed cases of dengue were encountered among American and British troops stationed in various countries bordering on the Mediterranean

Epidemics due to the importation of the virus and involving hundreds of thousands of people have occurred in areas where the mosquitoes capable of transmitting dengue fever were present notably Japan during World War II Greece in 1927–1928 and the Gulf Coast and adjacent Southern states of the U S A in 1922 (Fig 11)

Large epidemics of hemorrhagic fever due to dengue viruses of two

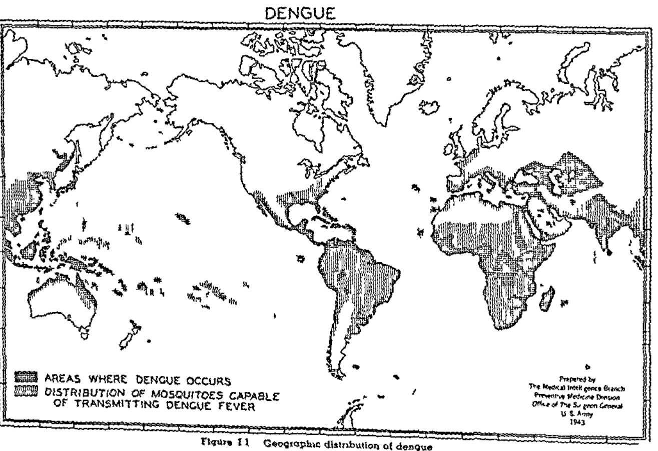


Figure 11 Geographic distribution of dengue

newly discovered serologic types have been studied in the Philippines and Thailand

Etiology The etiologic agent is a virus of the same order of magnitude as that of yellow fever approximately 17 to 25 mμ in diameter The virus is present in the patient s blood shortly before onset and in many instances throughout the entire febrile period The greatest concentration however has been found within the first 24 hours

There are four distinct immunologic types of the virus Types 1 and 2 from Hawaii and New Guinea respectively cause "classic" dengue Types 3 and 4 from Manila and Bangkok cause the hemorrhagic fever syndrome" The latter are attended by a high case fatality rate

Epidemiology Human beings possibly also certain species of monkeys in some regions and certain mosquitoes of the genus *Aedes* are involved in the cycle of infection by which dengue virus is known to be perpetuated in nature *Aedes aegypti Aedes albopictus* and *Aedes scutellaris* (also known as *Aedes hebrideus*) are the only proved vectors of the virus Epidemiologic observations in Polynesia suggest that *Aedes polynesiensis* may serve as a natural vector of dengue in that area *Aedes vexans Aedes sollicitans Aedes taeniorhynchus Aedes cantator Anopheles punctipennis Anopheles quadrimaculatus* and *Culex pipiens* did not transmit the infection under experimental conditions which permitted

quired an infective blood meal Under suitable conditions of temperature they can act as effective vectors for the rest of their lives which may be as long as one to three months A single infected mosquito can transmit the infection Since the virus is present in the blood of man or monkeys for only a few days it is clear that the disease is most likely to persist in those areas where the conditions are favorable for the survival of mosquitoes throughout the year It is for this reason that countries near the equator are probably the true permanent reservoirs of dengue and true endemic areas of the disease Although the newborn human population (after the first three to six month of life) in these equatorial endemic regions may be enough to keep the cycle of infection going from year to year it is possible that a jungle type of dengue fever depending on mosquito transmission among susceptible monkeys may also exist

Recent experimental work has shown that infection with dengue virus leaves a long lasting immunity Previous assumption that immunity to dengue may be variable or of short duration is probably best explained on the basis of the existence of more than one immunologic type of dengue Also the clinical diagnosis of dengue may not have been reliable when multiple attacks of the disease were assumed to have occurred in human beings under natural conditions Experimental studies on human volunteers have revealed that for a period of many months after recovery from infection with one type of dengue virus the individual may respond in a modified way to infection with another immunologic type of dengue virus Since at least two different types of the virus have been found to occur in a single epidemic area many febrile illnesses which clinically

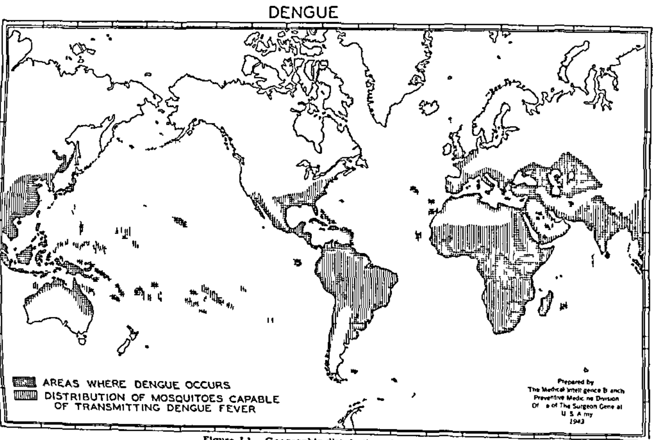


Figure 11 Geographic distribution of dengue

newly discovered serologic types have been studied in the Philippines and Thailand

Etiology The etiologic agent is a virus of the same order of magnitude as that of yellow fever approximately 17 to 25 mμ in diameter The virus is present in the patient's blood shortly before onset and in many instances throughout the entire febrile period The greatest concentration however has been found within the first 24 hours

There are four distinct immunologic types of the virus Types 1 and 2 from Hawaii and New Guinea respectively cause "classic" dengue Types 3 and 4 from Manila and Bangkok cause the "hemorrhagic fever syndrome" The latter are attended by a high case fatality rate

Epidemiology Human beings possibly also certain species of monkeys in some regions and certain mosquitoes of the genus *Aedes* are involved in the cycle of infection by which dengue virus is known to be perpetuated in nature *Aedes aegypti Aedes albopictus* and *Aedes scutellaris* (also known as *Aedes hebrideus*) are the only proved vectors of the virus Epidemiologic observations in Polynesia suggest that *Aedes polynesiensis* may serve as a natural vector of dengue in that area *Aedes vexans Aedes sollicitans Aedes taeniorhynchus Aedes cantator, Anopheles punctipennis Anopheles quadrimaculatus* and *Culex pipiens* did not transmit the infection under experimental conditions which permitted *A aegypti* to act as an effective vector *Aedes aegypti* mosquitoes require a minimum extrinsic incubation period of eight days and more usually 11 to 14 days before they are capable of transmitting the infection acquired in an infective blood meal Under suitable conditions of temperature they can act as effective vectors for the rest of their lives which may be as lon
mit the
keys for
sist in th
mosquitoes throughout the year It is for this reason that countries near the equator are probably the true permanent reservoirs of dengue and

year it is possible that a jungle type of dengue fever depending on mosquito transmission among susceptible monkeys may also exist

Recent experimental work has shown that infection with dengue virus leaves a long lasting immunity Previous assumption that immunity to dengue may be variable or of short duration is probably best explained on the basis of the existence of more than one immunologic type of

volunteers have revealed that for a period of many months after recovery from infection with one type of dengue virus the individual may respond in a modified way to infection with another immunologic type of dengue virus Since at least two different types of the virus have been found to occur in a single epidemic area many febrile illnesses which clinically

could not be diagnosed as dengue have been proved to be caused by dengue virus

Clinical Characteristics The classic syndrome of dengue is termed "dengue like" and will be described first followed by a description of the newly recognized hemorrhagic fever syndrome which is due to dengue viruses types 3 and 4

The usual incubation period is from five to eight days with a range of from two and one half to 15 days depending upon the amount of virus introduced Headache backache fatigue stiffness anorexia chilliness malaise and occasionally rash may appear six to 12 hours before the first *rise in temperature In about half the number of patients the onset is* sudden with a sharp rise in temperature severe headache pain behind the eyes backache pain in the muscles and joints and chilliness but only rarely a shaking chill Fever persists for five to six days in typical cases and usually terminates by crisis A saddleback or diphasic type of temperature curve is seen in some patients with dengue but is not observed in the majority and cannot be regarded as pathognomonic Anorexia and constipation are *common and epigastric discomfort* with colicky pain and abnormal tenderness of the abdomen may be seen Altered taste sensation also constitutes a common symptom early in the disease Marked weakness and dizziness photophobia drenching sweats sore throat cough epistaxis dysuria hyperesthesia of the skin pain in the groin and testicles and delirium are occasionally encountered The lymph nodes are frequently enlarged the spleen only rarely Nuchal rigidity is absent even when the patient complains of a stiff neck

[illegible] and rarely lasts for

after defervescence another type of eruption occurs in many patients This consists of small petechiae over the dorsum of the feet and legs and occasionally also in the axillae over the dorsum of the wrists hands and fingers and on the buccal mucosa and hard and soft palates

A typical example of the characteristic changes in the leukocytes is shown in Figure I 2 The most marked leukopenia occurs several days after onset of fever and is due to a diminution in the neutrophils The blood picture as a rule returns to normal within a week after defervescence

This clinical picture is characteristic of a primary infection with dengue virus It has been established by isolation of virus in human volunteers that mild febrile illnesses of from one to three days duration without rash may also be dengue these experiments also suggest that the most probable explanation *is that such individuals possess a partial* immunity resulting from previous infection with another immunologic type of the virus

The hemorrhagic fever syndrome has occurred in large epidemics in the Philippines and in Thailand with relatively high case fatality rates Bleeding from the nose and mouth and into the gastrointestinal tract was

Neither leukopenia nor leukocytosis characterized ca
rhagic fever syndrome, but there was thrombocytopeni
usually due to blood loss Fatal cases exhibited multiple
edema in many organs, particularly the heart

Diagnosis. Dengue should be suspected among
demic areas among recent arrivals from an area whe
endemic, and during epidemics in nonendemic region
tion of the virus and the presence of the vector mosqu

The virus in human blood is best preserved in the fro
state but it can also remain active for several weeks u

tests are available The dengue viruses have a group rel

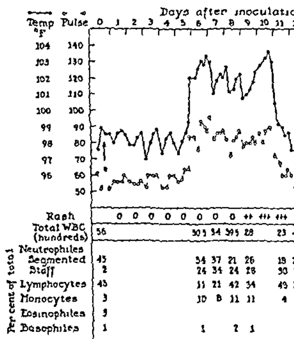


Figure 12. Graphic representation of temperature and pulse rate
inoculated experimentally with the Hawaiian strain of dengue virus

with the virus of yellow fever but also with the viruses of West Nile Japanese B encephalitis and St Louis encephalitis (see Table I 3 p 10) These relationships are more readily demonstrable by the hemagglutination inhibition and complement fixation tests than by the neutralization test However the neutralization test with specific antisera permits the

because the group specificity of their antigens is not likely to miss an infection with a hitherto unrecognized immunologic type of dengue virus

In the differential diagnosis one must consider influenza typhus measles rheumatic fever malaria and sandfly fever In endemic areas dengue may be difficult to distinguish from the early stages of yellow fever

Treatment Treatment is symptomatic

Prophylaxis Passage of the dengue virus in mice has produced a variant which still produces rash and immunity but has lost its capacity to cause any significant disease in human beings Although dengue vaccine prepared with such modified virus has proved effective in experimental studies it is not commercially available The type of antimosquito measures to be used are determined in large measure by whether *A aegypti* or *A albopictus* or both are the predominant mosquitoes in the area

Yellow Fever

Albert B Sabin

Synonyms Virus amaril fievre jaune gelb fieber

Definition An acute infectious endemic or epidemic disease caused by a filtrable virus transmitted by species of mosquitoes belonging chiefly to the genera *Aedes* and *Haemagogus* The disease is characterized by hepatic necrosis which tends to be midzonal in distribution and by a solid immunity after recovery Protective antibodies persist in the serum for many years if not for life

Distribution The disease is endemic throughout much of South America especially in the rain forests of the Orinoco Magdalena Altrato and Amazon watersheds It is also present along the southern coast of Bahia in Brazil and has been reported in northern Argentina and Ecuador during periodic waves of the disease Since 1948 yellow fever has advanced westward across Panama and northward through Costa Rica into southeastern Nicaragua Guatemala and finally into Mexico Human cases have occurred in northern Honduras and an outbreak of yellow fever was discovered in Trinidad in 1954 In Africa it extends from the west coast south of the Sahara through the Belgian Congo into northern Rhodesia Nyasaland Uganda, Kenya and Eritrea

Etiology. Strains of yellow fever virus obtained from different areas appear to be immunologically identical Recently isolated virulent strains injected into nonimmune rhesus monkeys produce a rapidly fatal disease with the characteristic lesions of yellow fever Intracerebral inoculation into mice produces a fatal encephalitis Serial intracerebral passage in mice transforms the natural viscerotropic virus into a fixed neurotropic strain which however retains the capacity to confer immunity

chus) Mosquitoes of the last three genera do not transmit the virus by bite Following the infecting blood meal there is an extrinsic incubation period of one to three weeks depending upon conditions of temperature and humidity in the course of which multiplication of the virus occurs The mosquitoes which can transmit the disease then become infective to a new host and the infection persists throughout the life of the mosquito Virus is recoverable from the blood of a patient with yellow fever during only the first three to five days of the disease

Epidemiology Yellow fever may be described as occurring in three forms The first of these occurs in classic epidemic outbreaks which are strictly urban and *A aegypti*-transmitted The second jungle yellow fever occurs in the absence of *A aegypti* It is endemic in certain jungle areas in South and Central America and Africa It becomes highly endemic or even epidemic in certain jungle regions when the human population is abundant and nonimmune The third form is the *Aedes* borne rural yellow fever which has occurred in certain sparsely populated areas in Brazil

Classic epidemic yellow fever is an urban disease transmitted by *A aegypti* It is characterized by an interval of two to three weeks between the arrival of an infected person and the first appearance of secondary cases This interval corresponds to the period of extrinsic incubation of the virus in the vector *A aegypti* This mosquito is domestic and is al

is transmitted by forest mosquitoes The animals have free virus in their blood for only a few days and rapidly become immune therefore it is improbable that there is a true animal reservoir The principal vectors are *Haemagogus spegazzinii* and its subspecies *falco H capricornii* and *Aedes leucocelaenus* It is believed that the virus survives the dry season in the adult mosquito Human disease is a casual episode occurring for the most part in persons clearing the jungle and is in consequence a disease primarily of young adult males rarely affecting women and children When the human population is abundant in an area where jungle yellow fever is endemic *Haemagogus* may act as a vector from man to man producing epidemic outbreaks

Jungle yellow fever in Africa is essentially a disease of monkeys *Aedes africanus* and *A leuteocephalus* appear to be the active vectors in the

monkey population whereas *A simpsoni* a semidomestic mosquito transmits the virus from monkey to man

In all areas where the disease is endemic mild unrecognized forms occur

Since recovery from the disease is accompanied by the development of a permanent solid immunity in both man and animals maintenance of the virus in an area depends upon a delicate balance of many factors The more important of these are the nature of the reservoir the species of vectors climatic and other factors affecting multiplication of the vectors and the number and distribution of nonimmune hosts Disturbance of this balance accounts for the disappearance of the disease from many areas where it has been prevalent in the past

The recent spread of the disease into Central America the increasing number of mosquito species which have been shown capable of harboring and transmitting the virus and the prevalence of proved vectors in the Far East are ample indications of the ominous threat that yellow fever constitutes for India and the Orient However two procedures permit accurate identification of the disease in time and place and appropriate quarantine measures and mass immunization of exposed population groups can be instituted The mouse protection test identifies immune individuals in the surviving population and analysis of the age groups from whom serum was taken indicates the time at which the infection was prevalent Similarly histologic examination of specimens of liver tissue obtained by the viscerotome provides conclusive proof of current disease without problems associated with routine postmortem examinations

Pathology The essential lesion is hepatic necrosis which in the

arenchymal

cytoplasm

ile stained

and degenerative changes are demonstrable in the spleen and myocardium Hemorrhages may be present in the skin gastrointestinal tract lungs and other organs

The pathologic physiology is characteristic and important

1 There is a rapid decrease in urinary output which may progress to severe oliguria This is accompanied by a rapidly diminishing excretion of chlorides

2 Increasing amounts of albumin and numbers of casts are present in *the urine in the early stages*

3 In severe cases peptonuria appears about the fourth day and increases in magnitude in fatal cases

4 Hypoglycemia may be severe and persistent

5 In severe cases there is an increase in the guanidine like substances in the blood

These changes revert to normal during convalescence

Clinical Characteristics There is great variation in severity ranging from instances of mild transitory fever to the exceedingly acute and rapidly fatal types The incubation period is usually three to six days After mild prodromal symptoms a moderate rise in temperature occurs

with elevation of pulse rate and blood pressure chilliness headache and bone aches The fever reaches a maximum of 104° F usually by the second day and remains elevated for another day or two Faget s sign—a falling pulse rate in the presence of a constant or rising temperature—appears in this primary febrile period After three to four days of fever in some instances the temperature falls to normal and is followed shortly by a secondary rise producing the characteristic saddleback fever curve Jaundice and hemorrhage may appear by the fourth or fifth day Ordinarily icterus is not intense even in severe cases Nausea and vomiting are common Gastrointestinal hemorrhage producing coffee ground vomitus the classic "black vomit" occurs in severe infections and is ominous The patient is usually mentally clear and often anxious and alert

The secondary rise of fever may terminate by crisis or lysis in the second week Most of the deaths occur from the fourth to the ninth day Relapses are rare and convalescence is usually rapid and without sequelae A permanent immunity is produced

Mortality The mortality rates in epidemics of yellow fever have reached as high as 50 per cent In endemic areas the death rate among the native population is usually 7 to 10 per cent

Diagnosis. The diagnosis of yellow fever on clinical grounds is easy in the presence of an epidemic Sporadic cases however may present difficult diagnostic problems The following points may be of value

1 In the initial stage there is a polymorphonuclear leukocytosis followed at the end of the first week by leukopenia with a rise of mononuclear cells
2 Increasing albuminuria and casts
3 Rapidly diminishing urinary chloride excretion
4 Hypoglycemia

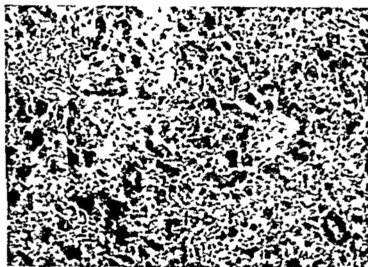


Figure 1.3 Section of liver in yellow fever Necrosis of parenchyma most intense in intermediate zones leukocytic infiltration.

monkey population whereas *A simpsoni* a semidomestic mosquito transmits the virus from monkey to man

In all areas where the disease is endemic mild unrecognized forms occur

Since recovery from the disease is accompanied by the development of a permanent solid immunity in both man and animals maintenance of the virus in an area depends upon a delicate balance of many factors The more important of these are the nature of the reservoir the species *of vectors climatic and other factors affecting multiplication of the vec*tors and the number and distribution of nonimmune hosts Disturbance of this balance accounts for the disappearance of the disease from many areas where it has been prevalent in the past

The recent spread of the disease into Central America the increasing number of mosquito species which have been shown capable of harbor ing and transmitting the virus and the prevalence of proved vectors in the Far East are ample indications of the ominous threat that yellow fever constitutes for India and the Orient However two procedures per mit accurate identification of the disease in time and place and appropri ate quarantine measures and mass immunization of exposed population groups can be instituted The mouse protection test identifies immune individuals in the surviving population and analysis of the age groups from whom serum was taken indicates the time at which the infection was prevalent Similarly histologic examination of specimens of liver tissue obtained by the viscerotome provides conclusive proof of current disease without problems associated with routine postmortem examina tions

Pathology The essential lesion is hepatic necrosis which in the

[illegible] The parenchymal

the cytoplasm

[illegible] bile stained

and degenerative changes are demonstrable in the spleen and myocar dium Hemorrhages may be present in the skin gastrointestinal tract lungs and other organs

The pathologic physiology is characteristic and important

1 There is a rapid decrease in urinary output which may progress to severe oliguria This is accompanied by a rapidly diminishing excretion of chlorides

2 Increasing amounts of albumin and numbers of casts are present in the urine in the early stages

3 In severe cases peptonuria appears about the fourth day and in creases in magnitude in fatal cases

4 Hypoglycemia may be severe and persistent

5 In severe cases there is an increase in the guanidine like substances in the blood

These changes revert to normal during convalescence

Clinical Characteristics There is great variation in severity rang ing from instances of mild transitory fever to the exceedingly acute and rapidly fatal types *The incubation period is usually three to six days* After mild prodromal symptoms a moderate rise in temperature occurs

with elevation of pulse rate and blood pressure chilliness headache and bone aches The fever reaches a maximum of 104° F usually by the second day and remains elevated for another day or two Faget s sign—a falling pulse rate in the presence of a constant or rising temperature—appears in this primary febrile period After three to four days of fever in some instances the temperature falls to normal and is followed shortly

curve

Ordi

miting

are common Gastrointestinal hemorrhage producing coffee ground vomitus the classic "black vomit occurs in severe infections and is ominous The patient is usually mentally clear and often anxious and alert

The secondary rise of fever may terminate by crisis or lysis in the second week Most of the deaths occur from the fourth to the ninth day Relapses are rare and convalescence is usually rapid and without sequelae A permanent immunity is produced

Mortality The mortality rates in epidemics of yellow fever have reached as high as 50 per cent In endemic areas the death rate among the native population is usually 7 to 10 per cent

Diagnosis The diagnosis of yellow fever on clinical grounds is easy in the presence of an epidemic Sporadic cases however may present difficult diagnostic problems The following points may be of value

1 In the initial stage there is a polymorphonuclear leukocytosis followed at the end of the first week by leukopenia with a rise of mononuclear cells
2 Increasing albuminuria and casts
3 Rapidly diminishing urinary chloride excretion
4 Hypoglycemia

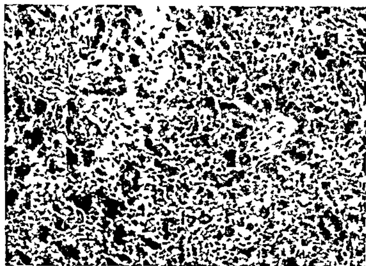


Figure 13 Section of liver in yellow fever Necrosis of parenchyma most intense in intermedia e zones leukocytic infiltration.

5 Peptonuria appearing about the fourth day of illness
6 Increase of the guanidine like substances in the blood

In the differential diagnosis one should consider malaria leptospiral jaundice infectious hepatitis relapsing fever and in mild cases dengue

Treatment There is no specific treatment Ample fluids should be administered together with glucose to combat the hypoglycemia Calcium relieves the symptoms of guanidine intoxication and should be given in the form of the gluconate 10 to 20 ml of a 7 5 per cent solution in glucose solution intravenously each day The prothrombin time should be determined during the course of treatment The administration of large doses of vitamin K as early as possible has been reported to be of considerable value

Prophylaxis The prevention of urban yellow fever entails four essential procedures

1 Elimination of the vector *A aegypti*
2 Prevention of importation of this vector by airplane or ship
3 Control of individuals entering from an endemic area
4 Vaccination of nonimmune persons

Aedes aegypti is a domestic insect frequenting the interior and immediate vicinity of houses where it also lays its eggs (for the details of control measures see p 767) Airplanes returning from endemic areas must be thoroughly sprayed with an efficient insecticide before they are opened and passengers or cargo released Similarly ships should be inspected and appropriate measures taken to eliminate *A aegypti* if present Unvaccinated individuals entering from regions where the disease is endemic should be held under control for a period equal to the incubation period of the disease three to six days

Efficient individual protection is conferred by administration of yellow fever vaccine Two vaccines have been developed each of which confers efficient and long lasting protection The American 17D vaccine is a living attenuated neurotropic virus grown in chick embryos It contains no human serum The desiccated vaccine is distributed in ampules which must be stored at a temperature below freezing until immediately before use It is then rehy' ' original volume diluted to to ensure even suspensio

One subcutaneous injection of 0 5 ml is given irrespective of the patient's age The vaccine produces an inapparent infection in most individuals About 5 per cent however have a slight febrile reaction on the fifth to the seventh day Protective antibodies are usually demonstrable in the blood about the tenth day The vaccine virus is not infective for mosquitoes The United States Public Health Service requires revaccination every four years

The Dakar mouse brain neurotropic virus vaccine has advantages and disadvantages It does not require storage under refrigeration and should be administered by scarification of the skin Systemic reactions occur in approximately 20 per cent of individuals immunized by this preparation by the scarification method The percentage is considerably higher when it is injected subcutaneously Some cases of encephalitis have followed its use

Rift Valley Fever

Albert B Sabin

Definition. A self limited febrile illness of several days' dur characterized by severe headache, malaise, leukopenia and rapic covery It is primarily a disease of sheep, cattle and other rumi mammals

Distribution. Rift Valley fever is restricted to certain parts of rica A sizable epidemic has occurred among both cattle and hu beings in South Africa

Etiology and Epidemiology. *The virus is present in the bloo* patients and is highly infectious for mice by inoculation by any r The mice usually succumb within about two days after inoculation most marked pathologic changes are in the liver

Except under special circumstances, it is inadvisable to work with virus in the laboratory or to attempt virus isolation from the blood of tients because of the extremely high incidence of laboratory infe among individuals working with it

The virus has been recovered from mosquitoes in nature belongir several species of the genera *Eretmapodites* and *Aedes*, *E chrysog* has been shown to be capable of transmitting the infection under ex mental conditions

Diagnosis. Rift Valley fever should be suspected in the pres *of a self-limited febrile illness in endemic or potentially endemic a* The diagnosis can best be established by demonstrating the appear of complement fixing or neutralizing antibodies in patients suspecte having this infection Antibodies have been demonstrated as earl four days after defervescence and are known to persist for many ye

Treatment. Treatment is symptomatic

Prophylaxis. Mosquito control where practical

Phlebotomus Fever

Albert B Sabin, Revised by Irving Gordon

Synonyms. Sandfly fever, pappataci fever, three day fever, mer influenza of Italy

Definition. A self limited, *Phlebotomus* transmitted illness ch terized by fever of short duration, severe headache, pain in the eyes, junctival injection, malaise and leukopenia

Distribution. Since the clinical diagnosis of phlebotomus fev not always reliable, one cannot be certain that the disease has occu

outside areas in which its definitely established vector *Phlebotomus papatasii* is known to occur The distribution of *P papatasii* is restricted to certain parts of Europe Africa and Asia that lie between 20° and 45° north latitude The disease is definitely known to occur in Italy along the Adriatic Coast of Yugoslavia Greece Malta Crete Cyprus Egypt Israel Syria Iraq Iran the coast of Crimea the Azov and Black Sea littoral certain provinces of central Asia in the U S S R and the northwest and central provinces of India Although other species of man biting *Phlebotomus* flies are known to occur in South America and some also in North America there is no evidence that sandfly fever occurs in the Western Hemisphere

Etiology and Epidemiology The disease is caused by a virus which is present in the blood of patients during a period of approximately 24 hours before onset of fever There are two distinct antigenic variants the Naples strain and the Sicilian strain The virus is small approximately 17 to 25 mμ in diameter Infection with one strain does not protect against subsequent infection with the other The suckling mouse and certain tissue culture cells are susceptible and are used as laboratory hosts

Phlebotomus papatasii is the only proved vector of the virus Secondary cases do not arise by contact in the absence of the vector *Phlebotomus papatasii* is a sand colored hairy midge about 2 to 3 mm long and 1 mm thick It can be recognized by the position of its wings which are usually elevated and spread to form a V Only the female of the species bites the usual biting hours are during the night and early morning Their flight which is more like a series of hops is said to be not more than 50 to 100 yards from their breeding ground They alight on stones and other obstacles in their approach to a house and after entry continue to hop about with long pauses before biting These peculiarities of the flight and movement of sandflies make them particularly vulnerable to residual DDT spray Although breeding spots are difficult to demonstrate typical sites are rubble loose soil cracks in embankments and other dark protected spots containing sufficient moist organic matter to provide a suitable place for the development of their larvae Sandflies thrive during the hot dry seasons the precise period varying in different parts of the world Thus the season of the disease in different regions may vary from April or early May through early October Some evidence has been presented for the transovarial transmission of the virus among sandflies However this is not easy to demonstrate or repeat Consequently the ultimate reservoir of the virus is still in doubt

The disease is probably widespread early in childhood among the indigenous populations of endemic areas and is largely unrecognized Phlebotomus fever has been a particular problem among recently arrived immigrants and troops Under suitable conditions the vast majority of newcomers to endemic areas develop the disease during the course of the season

Clinical Characteristics The average incubation period is from three to four days the range being from two and one half to nine days The onset as a rule is sudden The following signs and symptoms may be encountered headache burning sensation or pain in the eyes photo

phobia stiffness in neck and back backache pains in the joints and extremities anorexia nausea vomiting abdominal distress alteration or loss of taste sore throat epistaxis profuse sweating and chills or chilliness Constipation may occur during the first few days and diarrhea during convalescence In *approximately 85 per cent of the patients the fever is* of two three or four days duration Fevers lasting less than one day or occasionally as long as five to nine days may occur The pulse rate is at first elevated but then drops more rapidly than the temperature During convalescence an actual bradycardia may be present

There are probably no characteristic physical signs but conjunctival injection which is occasionally limited to the exposed portion of the ocular conjunctiva (Pick s sign) may be observed The exposed parts of the neck and chest appear erythematous often as though the patient had just been sunburned severely Although reactions to the bites of sandflies and occasionally urticaria or erythema multiforme may be encountered there is no true rash

Changes in the leukocyte count are similar to those encountered in dengue and other viral infections accompanied by leukopenia (Fig 14) The picture varies with the stages of the illness During the first day of the fever the total count may be within normal limits associated with a relative and sometimes absolute increase in the neutrophils which is due to an increase in immature cells During the first day *however a relative and absolute decrease in the lymphocytes occurs* During the next two or three days the number of neutrophils begins to drop and the immature cells increase to a point where they may outnumber the segmented cells (Fig 14) The greatest decrease in the total number of leukocytes may not be observed until the end of the febrile period or after defervescence While the neutrophils are decreasing the lymphocytes are rising to a point where they may constitute as much as 40 to 65 per cent of the total number of leukocytes The changes in the proportions of the cells at different stages of the disease are more important for diagnostic purposes than is a single total leukocyte count

No evidence of hepatic damage has been found by liver function tests Although there have been reports of pleocytosis during certain outbreaks of the disease there is no evidence that the virus of phlebotomus fever is responsible for it The duration of convalescence varies with the individual and the climate Marked uncontrollable transitory mental depression is occasionally encountered One or two cycles of recurrent fever during convalescence have been reported and similar febrile cycles have been encountered in approximately 5 per cent of the human volunteers The cause of these recurrent cycles of fever is unknown since *no virus has been found in the blood There have been no fatalities* among thousands of uncomplicated cases of the disease

Diagnosis Repeated differential leukocyte counts revealing the characteristic changes in the relative proportions of the cells at different stages of the disease are of practical value Confirmation by complement fixation tests of sera from both the acute and convalescent phase is of value in epidemics or retrospectively in isolated cases

During the hot dry seasons of the year a febrile illness among new

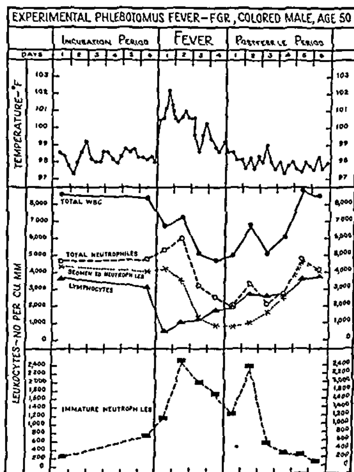


Figure 14 Differential white blood count in experimental phlebotomus fever (Sabin, Philip and Paul J A M A 125 1944)

comers in an endemic area should arouse suspicion of phlebotomus fever Differential diagnosis may be difficult The aseptic meningitis syndrome caused by poliomyelitis virus, the preicteric or nonicteric forms of infectious hepatitis, and influenza without associated respiratory signs may readily be confused with phlebotomus fever

Treatment. Treatment is symptomatic

Prophylaxis. Adult sandflies are very susceptible to DDT residual sprays, and large areas in Israel and Italy were freed of the disease when DDT was used primarily to control adult *Anopheles* Spraying of the breeding places with DDT may also kill the immature stages Spraying indoors with aerosol bombs containing pyrethrum will kill the adults Rubble, stone walls and other breeding and resting sites within 100 to 200 yards of human habitations should be removed or sprayed with DDT Suitable insect repellents applied to exposed skin areas will provide temporary individual protection

Japanese B Encephalitis

Albert B Sabin Revised by Irving Gordon

This virus has been recovered from human beings in Japan particularly south of Hokkaido and in Okinawa Guam Korea China Manchuria and the neighboring maritime provinces of the Soviet Union The virus of Australian X disease corresponds in most of its characteristics to that of Japanese B encephalitis and the Murray Valley encephalitis virus of Australia is closely related to it

Epidemiology Epidemics affecting thousands of people have occurred at varying and unpredictable intervals in Japan and lesser outbreaks have also been described from Okinawa Korea Manchuria

infected without neurologic involvement for every case of encephalitis that is recognized

Japanese B encephalitis has probably also occurred on Formosa and in Vietnam Java the Philippines the Malay Peninsula and Sumatra

Extensive studies indicate that *Culex tritaeniorhynchus* is the only vector in Japan and the seasonal incidence of epidemics of Japanese B encephalitis bears a precise relationship to the rise and fall of the numbers of *C tritaeniorhynchus* mosquitoes As one might expect the peak of the epidemic period is separated from the peak of the mosquito population by a period of one to two weeks which corresponds in part to the extrinsic incubation period of the virus in the mosquitoes and in part to the intrinsic incubation period of the infection in man By the time an epidemic is thoroughly established the number of *C tritaeniorhynchus* mosquitoes may already be quite small and at the termination of the epidemic it may be difficult to find these mosquitoes in appreciable numbers

Culex gelidus has been found infected with the virus in Malaya *Culex vishnui* was demonstrated to be naturally infected in the area of a recent outbreak in India

Diagnosis It has not proved possible to confirm reports that the virus can be recovered from the blood cerebrospinal fluid urine feces or saliva of patients with the disease Complement fixation and hemagglutination inhibition tests are the serologic procedures of choice for establishing the diagnosis A significant rise in titer of these antibodies may be demonstrated as early as seven to ten days after onset of the first symptoms Where dengue occurs serologic cross reactions with antibodies to that virus complicate the interpretation of complement fixation tests and consequently specific neutralization tests must be performed to confirm the diagnosis serologically

The diagnosis of the infection in a fatal case may be established most

rapidly by transmitting the infection to mice by intracerebral inoculation of human brain tissue and then preparing a complement fixing antigen from the brains of mice which succumb

3

Enterovirus Infections, Including Poliomyelitis

Irving Gordon

Introduction

Largely as a result of the concentrated research on poliomyelitis and related diseases during the past two decades the term "neurotropism" is presently used to denote virulence factors of virus strains that allow them under certain conditions to multiply in and perhaps damage the central nervous system The poliomyelitis viruses are an example Although most strains possess neurotropic properties central nervous system involvement in man is a relatively infrequent event compared *with the number of enteric or respiratory infections induced by poliomyelitis* viruses Furthermore some strains of poliomyelitis virus are only weakly neurotropic

The investigations of poliomyelitis that led to the development of this concept also led to the discovery of a large number of new viruses These new agents resembled the poliomyelitis viruses in so many respects that all have finally been grouped together as the *enteroviruses* First the Coxsackie viruses were discovered then the ECHO viruses It was well known that poliomyelitis virus could be obtained from feces of cases *However it was during studies of poliomyelitis like diseases that* laboratory investigations of fecal specimens resulted in the discovery and characterization of these two new virus groups The term enteroviruses appears to be well chosen as it emphasizes one of the most important properties of this group of viruses

The individual viruses that comprise the enterovirus group are all approximately 25 to 30 mμ in diameter As would be expected of agents that can survive and multiply in the gastrointestinal tract the enteroviruses are highly resistant to many physical conditions and chemical agents that *destroy other viruses For example they resist the action of* bile and bile products such as sodium desoxycholate which will inactivate the arthropod borne viruses Again unlike the arthropod borne

viruses the enteroviruses will survive in feces at summer temperatures and if organic material is present they resist chlorination They also survive the acid pH of the stomach and maintain viability for long periods under refrigeration

Several of the enteroviruses notably the poliomyelitis virus have been isolated in crystalline purity and those that have been studied sufficiently are found to consist of a central core of ribonucleic acid surrounded by a protein coat The core has been demonstrated to be infectious the protein coat, which is responsible to a great extent for the antigenicity of the various virus strains appears to protect the core against the environment and to be responsible for the ability of the virus particle to adsorb to and penetrate cells The protein covering therefore helps to determine host range and the pathogenesis of the diseases induced by these viruses

[illegible] example [illegible] infections [illegible] two or more enteroviruses in a single fecal specimen Finally enterovirus infections are ubiquitous From a practical point of view it can be expected that a given patient will have had more than one enterovirus infection by the time he has become an adult Since the fecal oral route is highly efficient in spreading the enteroviruses in a population the age at which a given population group acquires an enterovirus infection such as poliomyelitis depends to a great extent upon socioeconomic conditions In areas where high sanitary standards and practices are the rule the spread of enterovirus infections is slower and less complete than in populations with poor sanitation

On epidemiologic grounds it is apparent that the fecal oral route of transmission cannot be the only avenue by which the enterovirus infections are spread Droplet transmission is probably important especially in the temperate zones Furthermore the seasonal variation in incidence of enterovirus infections has not been fully explained but they are certainly spread from human to human by contact No vector has been demonstrated

Poliomyelitis

Albert B Sabin Revised by Irving Gordon

Synonyms Acute anterior poliomyelitis infantile paralysis

Distribution. Poliomyelitis occurs throughout the world wherever human beings live in large enough numbers or in sufficiently close contact with other regions to maintain the chain of transmission

Etiology. There are three antigenically distinct types of poliomyelitis virus types 1, 2 and 3 All three types consist of a ribonucleic acid core surrounded by a protein coat and are approximately 28 $m\mu$ in diameter Their differences in antigenicity are largely due to differences in their protein coats In neutralization tests, types 1 and 3 cross react with type 2 to a much greater extent than with one another This is of epidemiologic importance In contrast, a complement fixation antigen can be extracted from any one of the three types that will cross react with the other two types This is useful in diagnosis Strains within a given type vary greatly in virulence, which is largely dependent on the degree of neurotropism of the particular strain

Epidemiology. As has been stated above, poliomyelitis in human beings appears to be primarily an infection of the alimentary tract and only occasionally a clinically recognized disease of the nervous system Human stools are the richest source of the virus in nature Although the virus can be demonstrated in material obtained by swab or washings from the posterior pharyngeal wall, there is reason to doubt that under ordinary conditions it reaches the external environment by means of droplets from the mouth The many direct and indirect routes by which human feces may be transmitted from one individual to another constitute the potential modes of transmission of the infection among human beings

Experimental evidence has demonstrated that dosage is an important factor determining the outcome of infection The incidence of paralysis following ingestion of large doses of virus is very much higher than after ingestion of small doses Conversely, the incidence of inapparent or clinically mild or unrecognized types of infection is very much greater after the repeated ingestion of minute amounts of virus

believe that factors relating to the virulence of the various strains of virus and the amount ingested play a more important role in determining the incidence of paralysis and the occurrence of epidemics

The incidence of paralytic poliomyelitis in certain population groups over a period of many years appears to be inversely proportional to the amount of virus that is being disseminated among them This is one of *the seeming paradoxes in the epidemiology of the disease* Thus, antibody studies have shown that the incidence of paralytic poliomyelitis among populations exhibiting the highest incidence of inapparent or clinically unrecognized infections in the very early age groups is relatively much lower than in countries with advanced sanitation and hygiene In the former areas epidemics or large outbreaks of the disease are rare or practically unknown It has been suggested, therefore, that poor sanitation and hygiene which afford ample opportunity for transmission of the virus likewise provide a greater opportunity to acquire the inapparent or very mild type of infection by exposure to strains of low virulence and repeated exposure to small doses of virus This would create a population predominantly immune at a time when more virulent

ains of virus were introduced It would explain the relative absence outbreaks or epidemics in such communities at a time when new mers resident in the same areas experience a high attack rate of ralytic poliomyelitis

According to this view epidemics occur when strains of virus of higher ulence invade population groups that have been insufficiently im inized by strains of lower virulence belonging to the same immuno gic type

Pathology The pathogenesis of central nervous system involve

h is probably

place in the

consistently

r to onset of

urologic manifestations Within approximately a week the virus is no nger excreted from the pharynx but it continues to be present in the ools for several weeks even though circulating antibody levels are ually high by this time

It is thought that possibly the virus multiplies in lymphoid tissue for ample in tonsils or in Peyer s patches and that it then enters the ood At this stage antibody is highly effective in preventing further read If there is sufficient viremia however the "blood brain barrier" overcome and the central nervous system is invaded It is possible erefore to prevent the distressing central nervous system manifesta ons of poliomyelitis infection if relatively small amounts of neutralizing ntibody are present in the blood

In the central nervous system the anterior horn cells of the spinal ord are the classic location for lesions but other areas of the cord and metimes the dorsal root ganglia may be damaged In the brain the ortex is not usually involved except for the precentral motor cortex euronal destruction with neuronophagia is the classic neurologic sion If neurons are not completely destroyed recovery of function is ossible and this is important clinically Perivascular cuffing and in asion of areas of neuronal destruction by lymphocytes are characteristic f poliomyelitis Poliomyelitis virus may attack muscle directly and may ause myocarditis

Clinical Characteristics There are three characteristic clinical yndromes (1) abortive poliomyelitis (2) nonparalytic poliomyelitis nd (3) paralytic poliomyelitis These terms which denote severity also uggest progression of the infection and in fact poliomyelitis may rogress through the three stages consecutively The course may be iphasic with a partial or complete remission separating the preliminary minor illness from the later central nervous system involvement par icularly when the latter is of the severe paralytic form

The incubation period of poliomyelitis is usually between one and wo weeks but may range between four days and five weeks The onset s often gradual and the disease may develop slowly through the stages lescribed above

Abortive poliomyelitis is the most common type of clinical infection The patient suffers fever or feverishness chilliness malaise headache

nausea constipation and sore throat Sometimes there is vomiting The severity of the headache may be out of proportion to the rest of the symptom complex and may help to direct attention away from the tentative diagnosis of influenza or other syndromes that mimic influenza

Nonparalytic poliomyelitis progresses to involvement of the meninges the syndrome suggesting aseptic meningitis Headache is severe there is stiffness of the neck and back and Kernig s or Brudzinski s sign can be elicited There is pleocytosis of the cerebrospinal fluid predominantly polymorphonuclear leukocytic at first later it is almost entirely lymphocytic There is no change in the sugar content but there is an increase in protein Patients recover without neurologic residuals

Paralytic poliomyelitis is usually preceded by the abortive form but sometimes onset is so rapid that the various stages merge Paralysis is usually flaccid resulting from lower motor neuron involvement There is often considerable localized pain and muscle spasm which should not deter the physician from the diagnosis

Diagnosis Only full blown paralytic poliomyelitis or in some cases bulbar poliomyelitis without paralysis of respiratory muscles can be diagnosed clinically with assurance Diagnosis of influenza like minor illness is virtually impossible although during episodes of "summer grippe that run through a community poliomyelitis might be strongly suspected Diagnosis of the aseptic meningitis syndrome is likewise impossible without laboratory confirmation During epidemic periods however the vast majority of cases of aseptic meningitis syndrome are caused by poliomyelitis virus or by other enteroviruses and there is abundant evidence to indicate that the minor febrile illnesses that occur among contacts of poliomyelitis cases are also due to infection by the virus

Laboratory aids in diagnosis are isolation of the virus from fecal specimens and the detection of a rise in antibody titer by means of neutralization or complement fixation tests Specimens for isolation of virus should be refrigerated or frozen A properly taken rectal swab can be as useful as a large stool specimen The acute phase specimen of serum should be obtained as soon as possible after onset since antibodies rise rapidly in poliomyelitis The second specimen should be obtained three to four weeks after onset of illness

Treatment. Treatment is not specific but is chiefly symptomatic The patient should be kept in bed for the duration of fever and for several days thereafter thus diminishing the likelihood of paralysis or its severity *should it develop In paralytic patients who have an involve*ment of the spinal cord which may lead to paralysis of the muscles of respiration the availability of proper respirator care may prove life saving In patients with manifestations which make it difficult to keep the airway patent a tracheotomy may be indicated

Prophylaxis Vaccination will prevent poliomyelitis The only vaccine commercially available is formalin inactivated It contains all three types of virus At least four inoculations over a period of several years are required to afford optimum protection with formalin inactivated vaccine Since the virus must undergo prolonged exposure to relatively high concentrations of formaldehyde to ensure inactivation antigenicity of the

vaccine can be correspondingly diminished The multiple injections with the "boosters" given after an interval of months induce the recall phenomenon and accordingly good antibody levels are attained even with vaccines possessing small antigenic mass

Live attenuated vaccine that is administered by mouth has been used in large scale field trials These vaccines induce intestinal infection but cause no neurologic manifestations and result in satisfactory antibody responses *It is possible that in the future a schedule involving the use* of both live attenuated and of inactivated poliomyelitis vaccine will be utilized

Unvaccinated persons who are heavily exposed should be passively immunized by administration of 0 2 ml of gamma globulin per kilogram of body weight

Coxsackie Virus Infections
Herpangina, Epidemic Pleurodynia and Aseptic Meningitis

Irving Gordon

Introduction

The Coxsackie viruses occur in two groups group A contains 25 numbered antigenically distinct viruses group B contains five antigenically distinct viruses which are also assigned numbers The viruses closely resemble the poliomyelitis viruses in their physical and other properties They differ from the polioviruses in that they are highly infective for newborn mice Like polioviruses however they will also grow in a variety of tissue cultures

Viruses of group A are recognized by their ability to produce diffuse marked myositis and destruction in the skeletal musculature of suckling mice The mice die because of their inability to breathe Group B viruses are also capable of producing myositis but it is focal and less severe In mice group B viruses also induce encephalitis and myocarditis and sometimes cause lesions in the pancreas and liver

Epidemiology The epidemiology of Coxsackie virus infection closely resembles that of poliomyelitis It is important to note that poliomyelitis and Coxsackie virus infections may coexist in epidemics that double infections occur and that Coxsackie virus group A infections probably increase the severity of simultaneous poliomyelitis in man During an outbreak in which a given clinical form of Coxsackie virus infection predominates it is common to observe other clinical variants in a given epidemiologic unit For example pleurodynia and aseptic

meningitis due to the same type of Coxsackie virus group B could occur within a family

Pathology The pathogenesis of Coxsackie virus infections in man has not been worked out completely, but is thought to resemble that of poliomyelitis in many respects Viremia is more marked and more prolonged in Coxsackie virus infections than in poliomyelitis Whereas poliomyelitis virus can rarely be recovered from cerebrospinal fluid Coxsackie viruses of group B can be recovered from the cerebrospinal fluid of patients with aseptic meningitis with sufficient frequency to be useful diagnostically

While myositis is prominent in experimentally infected suckling mice particularly in group A infections and has also been demonstrated in a few human cases there is still relatively little evidence that Coxsackie viruses cause widespread or severe damage of skeletal muscle in man However both myocarditis and encephalitis are important manifestations of group B infections of humans The former may be fatal to infants and the latter may be followed by residual weakness of involved muscle groups Poliomyelitis like lesions of the spinal cord have been demonstrated in infected monkeys

Herpangina

Definition Herpangina is a self limited febrile illness of several days duration associated with vesicular or ulcerative lesions in the posterior region of the mouth and in the throat It is caused by a number of types of Coxsackie viruses of group A

Clinical Characteristics The disease occurs predominantly among children generally during the summer and early autumn months in the temperate zone The characteristic lesions appear as minute vesicles or small punched out ulcers surrounded by red areolas From two to 20 may be present on the anterior pillars of the fauces the pharynx and the palate Dysphagia may be marked Systemic manifestations may include anorexia vomiting and occasionally prostration The prognosis is good no fatalities have been reported

Diagnosis The clinical manifestations are so pathognomonic that presumptive diagnosis may be made immediately Laboratory confirmation of infection is usually omitted except in outbreaks Procedures are the same as in poliomyelitis

Treatment Treatment is symptomatic and should include proper oral hygiene

Epidemic Pleurodynia

Synonyms Bornholm disease devil s grip epidemic myalgia

Definition Epidemic pleurodynia is a self limited febrile illness characterized by headache malaise anorexia and severe thoracic or abdominal pain that is worse on respiration It is caused by group B Coxsackie viruses of any type There have been no fatalities The symptoms may be explained by evidence indicating that the infection is generalized and that localized pain is due to diaphragmatic involvement

Epidemiology and Clinical Characteristics Large outbreaks have occurred in Europe and the United States The disease is important in tropical medicine only because sporadic cases are likely to be misdiagnosed and since the sudden onset of severe chest or abdominal pain is typical the disease can be mistaken for a serious medical or surgical emergency The disease is most common in children and young adults but also occurs in older persons Epidemics are limited to summer or early autumn in temperate climates but the high prevalence and wide distribution of the Coxsackie viruses make sporadic infection possible at any time in the tropics Spread is by contact and multiple cases are observed in families Associated cases of infection by the causative group B virus type may exhibit one of the other syndromes incited by group B viruses especially aseptic meningitis

Shifting pain difficult for patients to pinpoint is localized in the epigastrium and lower thorax and is worse with motion including respiration It may be unbearable but may remit and recur and the temperature may fluctuate with the pain Signs of consolidation are absent but friction rubs are occasionally heard on auscultation Gastrointestinal symptoms are typical in children Relapses sometimes multiple may occur after recovery Orchitis is the chief complication

Diagnosis Clinical laboratory findings are of no help except to rule out other diseases Virus diagnostic laboratory aids are the same as in poliomyelitis

Treatment Treatment is symptomatic Once the diagnosis is made the patient should be reassured as to eventual recovery but cautioned that symptoms may recur and warned that premature activity is to be avoided

Aseptic Meningitis

As has been mentioned the group B Coxsackie viruses are more frequently the cause of aseptic meningitis than the group A viruses Onset may be abrupt or gradual and may resemble that of abortive poliomyelitis so closely that differential diagnosis must depend on laboratory aids After anorexia malaise nausea and abdominal discomfort localizing meningeal signs appear In addition there may be muscle aches. Commonly the fever may drop before onset of fully developed symptoms and signs referable to the meninges Complete recovery is the rule Sometimes however the brain or cord is involved and residual weakness may result

Myocarditis and Pericarditis

Coxsackie viruses of group B can cause fatal myocarditis in newborn infants Fatal cases develop signs of circulatory failure with increased pulse rate and cyanosis Virus can be recovered not only from the heart but also from the brain at necropsy

Pericarditis in adults has also been demonstrated to be due to Coxsackie infections

The ECHO Virus Diseases Aseptic Meningitis, Epidemic Exanthem, and Epidemic Infantile Diarrhea

Irving Gordon

The ECHO viruses closely resemble the polioviruses and Coxsackie viruses They are classified apart chiefly because of their restricted host range they can be propagated in the laboratory only in tissue cultures prepared from human or monkey cells Similar viruses however, are found in lower animals The different members of the group vary in virulence and there is accordingly considerable variation in the clinical characteristics of ECHO virus infection The term ECHO was coined from the initial letters of Enteric cytopathogenic human orphan at the time these viruses were not known to be causes of disease There have been some difficulties in choosing between the Coxsackie and ECHO groups for classification of certain viruses ECHO virus type 9 which was responsible for widespread epidemics of aseptic meningitis with or without rash in Europe and the United States in 1956 and 1957 does cause myositis and paralysis in mice similar to that produced by Coxsackie viruses of group A and some ECHO strains of type 10 also can infect mice It is possible that the terminology will be changed as our knowledge of these viruses increases

The epidemiology pathogenesis and pathology of the ECHO virus infections resemble those of the other enteroviruses Virus may be recovered from feces or from pharyngeal secretions and like the Coxsackie group B viruses ECHO viruses of certain types can also be recovered from the cerebrospinal fluid of some patients with aseptic meningitis

Clinical Characteristics *Epidemic Exanthem with or without Aseptic Meningitis* In addition to the aseptic meningitis syndrome a maculopapular rash often in association with conjunctivitis and influ

virus infections particularly

morbilliform rubelliform or

18 has been demonstrated to be the cause of an outbreak of watery diarrhea among newborn infants in a nursery It was also recovered from asymptomatic adult contacts

Respiratory Enteric Syndrome A respiratory enteric illness has been shown to be due to ECHO viruses types 8 and 20 Fever lasting for two days nasal discharge and serous exudate from the eyes vomiting

and watery malodorous stools were observed in infants less than two years of age Several viruses known to cause symptoms of common respiratory disease without alimentary involvement resemble the ECHO viruses closely and it is likely that they will be classified as members of the ECHO group in the near future

4

Other Virus Diseases of Special Importance or Interest in Tropical or Subtropical Areas

Rabies

Albert B Sabin Revised by Irving Gordon

Synonyms Hydrophobia rage lyssa rabbia rava tollwut

Definition Rabies is an acute infectious disease caused by a virus It primarily involves the central nervous system and is characterized by hyperexcitability pharyngeal spasm convulsions and a fatal outcome

Distribution The disease is widely disseminated throughout all areas of the world with the exception of Australia and Hawaii where enforcement of quarantine measures before large urban centers developed prevented its entry Scandinavia and the British Isles have eradicated the disease and the Netherlands Switzerland and Canada are also relatively free of it

Etiology and Epidemiology Rabies exists in an enzootic form in wild animals and in the dog The virus present in the saliva is transmitted by the bite of an infected animal An increased prevalence of human cases of the disease often is a reflection of epizootic conditions in the dog population or the sylvan reservoir Vampire bats are a source of human infection in some areas

Pathology Lesions characteristic of neurotropic viral infections are present in the central nervous system chiefly in the medulla the basal ganglia motor cortex and the posterior horns of the spinal cord When present the characteristic inclusions Negri bodies are pathognomonic They are frequently absent in infections with certain strains of the virus

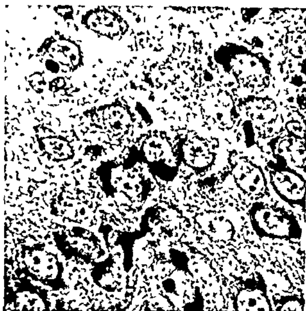


Figure 15 Intracytoplasmic inclusion bodies Negri bodies of rabies

The Negri body is a globular or ovate, acidophilic, intracytoplasmic structure with a maximum size approximating that of a red blood cell The larger bodies often contain basophilic material

Clinical Characteristics. The incubation period is highly variable, ranging from ten days to more than seven months It is believed that the virus reaches the brain along neural pathways and that the location of the bite is a factor determining both incubation period and severity Slight to moderate fever, occipital headache, malaise anorexia vomiting and abnormal sensations in the region of the infecting bite mark the onset of disease Hyperesthesia and mental and neuromuscular hyperexcitability develop rapidly, together with stiffness of the neck and violent spasms of the muscles of deglutition and of the accessory muscles of respiration The mere sight, smell or sound of liquid stimulates this reflex The acute excitability progresses to generalized convulsions and death usually occurs during a seizure A clinical variant, often associated with bites on the toes, particularly those inflicted by vampire bats, presents the picture of an ascending paralysis with little or no hyper excitability or difficulty in swallowing In both forms the disease is invariably fatal

Diagnosis. The characteristic clinical picture and history of exposure should suggest rabies Definitive intravitam diagnosis may be made by isolation of the virus from saliva or by demonstration of neutralizing antibodies when vaccine has not been administered Demonstration of Negri bodies in autopsy material or recovery of the virus establishes the diagnosis (Fig 15)

The intermittent nature of the muscle spasm aids in the differentiation from tetanus

Treatment. Treatment is supportive and symptomatic Barbiturates are recommended in preference to morphine for sedation An attempt should be made to maintain fluid balance Recovery is most unlikely

Prophylaxis. The prevention of rabies is based upon (1) observations and study of the suspect animal, and (2) care of the patient It is important to avoid delay in both

Observation of the Animal It is imperative that the animal which inflicts the bite should not be destroyed Instead, it should be observed, preferably by a veterinarian If typical signs are not apparent, or death does not occur within ten days, the animal could not have transmitted rabies In contrast, when a clinical disease suggestive of rabies develops, the animal should be sacrificed, and its intact refrigerated head should be delivered forthwith to a competent diagnostic laboratory Delay en route may render specimens useless Impression smears of the brain should be taken in the laboratory, if Negri bodies are demonstrated a tentative diagnosis can be made It is good practice, however, to confirm

with a specimen of the

amination has revealed

Care of the Patient This consists of *treatment of the wound* and *immunization*

Local treatment of the wound is probably highly effective, and a most important technique for preventing the disease The object is to wash away or inactivate deposited virus Soap or detergent will accomplish this in open wounds but not in puncture wounds The latter must be cauterized with nitric acid

The Expert Committee on Rabies of the World Health Organization has outlined the indications for specific prophylaxis of rabies after exposure (Table I 4)

Passive immunization by administration of hyperimmune antiserum is unquestionably of great value Serum reactions occur, and precautions should be taken to determine whether the patient is sensitive before serum is administered

Unlike the original attenuated living vaccines, the vaccine preparations currently in use are inactivated by phenol or by ultraviolet light Daily injections of 2 ml are given for two weeks The postvaccinal encephalomyelitis that sometimes develops is not due to rabies virus, it is caused by a sensitivity reaction to the nervous tissue from which the vaccine derives Therefore, if a course of rabies vaccination is begun, it should be interrupted if even trivial signs of central nervous system impairment develop

Vaccines have been made from virus grown in duck and chick embryos The duck embryo vaccine has been licensed and is commercially available in the United States The brain tissue vaccine should be used when systemic antiserum is indicated since duck embryo vaccine has not been tested in persons also given antiserum The use of duck embryo vaccine may be considered in instances of mild exposure, particularly in persons immunized previously, and to complete a course of treatment

Table 14. Recommendations of the Expert Committee on Rabies of the World Health Organization for Prophylaxis after Exposure

NATURE OF EXPOSURE	CONDITION OF ANIMAL* AT TIME OF EXPOSURE	CONDITION OF ANIMAL* DURING OBSERVATION PERIOD OF 10 DAYS	RECOMMENDED TREATMENT**
I No lesions Indirect contact only	Rabid	—	None†
II Licks 1 *Unabraded skin*	*Rabid*	—	None†
2 Abraded skin scratches and abraded or unabraded mucosa	(a) Healthy	Healthy	None
	(b) Healthy	Clinical signs of rabies or proved rabid	Start vaccine at first signs of rabies in animal
	(c) Signs suggestive of rabies	Healthy	Start vaccine immediately Stop treatment if animal is normal on fifth day after exposure‡
	(d) Rabid escaped killed or unknown	—	Start vaccine immediately
III Bites 1 Simple exposure	(a) Healthy	Healthy	None
	(b) Healthy	Clinical signs of rabies or proved rabid	Start vaccine at first signs of rabies in animal
	(c) Signs suggestive of rabies	Healthy	Start vaccine immediately Stop treatment if animal is normal on fifth day after exposure‡
	(d) Rabid escaped killed or unknown or any bite by wolf jackal fox bat or other wild animal	—	Start vaccine immediately
2 *Severe exposure (multiple or face head or neck bites)*	*(a) Healthy*	*Healthy*	*Hyperimmune serum immediately No vaccine as long as animal remains normal*
	(b) Healthy	Clinical signs of rabies or proved rabid	As in III 2 (a) but start vaccine at first sign of rabies
	(c) Signs suggestive of rabies	Healthy	Hyperimmune serum immediately *followed by vaccine* Vaccine may be stopped if animal is normal on fifth day *after exposure*
	(d) Rabid escaped killed or unknown Any bite by wild animal or bat	—	Hyperimmune serum immediately followed by vaccine

* These indications apply equally well whether or not the biting animal has been previously vaccinated
** Hyperimmune serum to be effective must be given within 72 hours of exposure
† *Start vaccine immediately in young children and patients where a reliable history cannot be obtained*
‡ Alternative treat*ment would be not to give hyperimmune serum and not start vaccine as long as animal remained normal*

in individuals showing signs of neuroparalysis Further study is required *to determine if the antibody levels induced by avian vaccines are as high* as those obtained by brain tissue vaccine

Control Effective measures for control include licensing of dogs *destruction of strays quarantine of imported dogs confinement* and observation of a dog guilty of unprovoked biting and of all canine contacts of a rabid animal quarantine or muzzling of all dogs for six months after the last reported case reduction of the wild animal reservoir and compulsory vaccination of dogs when quarantine cannot be effectively enforced or where exposure to an endemic wild animal reservoir exists

Mumps

This virus should be suspected as a cause of the aseptic meningitis syndrome in individuals with or without evidence of involvement of the *salivary glands when there is a history of recent exposure to mumps or* during a period when mumps is epidemic in the community

Diagnosis The diagnosis can best be established by complemen

meningitis it is not recommended as a diagnostic procedure for routine purposes

Herpes Simplex

manifestations of infection by herpes simplex virus It should be kept in mind however as a possible cause of severe and often fatal meningo encephalitis not only in children but also in adults

Diagnosis In surviving patients the diagnosis can be established by serologic procedures and in fatal cases by the demonstration of acidophilic intranuclear inclusions in various types of cells in the nervous system and by isolation of the virus in mice or eggs

Smallpox

Col Arthur P Long Revised by Irving Gordon

Synonyms Variola (major and minor) alastrim amaas Kaffir milk pox West Indian modified smallpox para smallpox

Definition Smallpox is an acute infectious communicable virus disease usually characterized by severe toxemia and a single crop of skin lesions which typically progress through macular papular vesicular and pustular stages In the purpura variolosa variety of variola major the skin eruption does not develop

Distribution The disease is endemic throughout the world Asia Africa and the Middle East are particularly important foci It is most prevalent in those areas in which vaccination is not practiced or is not successful if performed

Etiology and Epidemiology Elementary or Paschen bodies demonstrable in the fluid of the skin lesions are virus particles When appropriately stained they are visible with the ordinary microscope and measure about 200 mμ in diameter Epithelial cytoplasmic inclusions Guarnieri bodies found in variola infections are believed to represent intracellular aggregates of virus

The virus is relatively stable and is resistant to drying It is present in the upper respiratory tract of the patient or in the skin lesions which retain the virus until they are healed Scales and desquamated epithelium harbor viable virus for long periods

Transmission is from man to man usually directly by contact or by

respiratory droplets or droplet nuclei However indirect spread may occur through contact with contaminated clothing bedding or other articles which have been in contact with the patient

Smallpox is highly contagious ranking with measles and chickenpox in this respect All persons in the immediate environment (hotel hospital barracks ship etc) must be considered contacts exposed to infection Susceptibility is universal and is altered only by a prior attack of the disease or by successful vaccination

Pathology The virus enters the body through the upper respiratory tract and in the susceptible individual multiplies locally Viremia follows with dissemination of the virus to the viscera and particularly to the skin and certain other epithelial surfaces where multiplication continues

The typical focal lesions develop in the skin Degeneration and separation of cells of the epidermis and exudation result in vesicle formation The vesicle is multilocular and umbilicated The lesions are deeply situated within the skin In the course of several days the vesicle fluid becomes cloudy and subsequently purulent forming the pustule This progression may be modified however by the use of antibiotics and the lesions may develop from the vesicular to the desiccated stage without becoming pustular

Other organs than the skin are also affected and show inflammatory reactions cloudy swelling and at times focal hemorrhages

In the severe fulminating hemorrhagic form of the disease purpura variolosa there is massive intracutaneous hemorrhage as well as mucosal hemorrhages in the kidney gums and oral mucous membranes In this form the blood findings include thrombopenia a high leukocytosis with many young granulocytes including blast cells and anemia

Clinical Characteristics The incubation period is usually about 12 days with extremes of six to 22 days Ordinarily the onset is abrupt with sharply rising temperature following chills or chilly sensations and accompanied by symptoms of severe toxemia headache nausea and vomiting and severe general aching that is most pronounced in the back muscles Marked prostration is common

This stage of invasion usually continues for two or three days during which a prodromal flushing or rash may appear During this period also the generalized violaceous erythematous blush of purpura variolosa appears and is an exceedingly bad prognostic omen It is usually followed immediately by hemorrhagic phenomena and death ensues before the appearance of the typical eruption

The characteristic skin lesions commonly appear about the fourth day accompanied by subjective and objective improvement in the patient's condition The lesions at first are macular soon becoming papular and within a few days vesicular In the absence of antibiotic therapy the pustular stage is reached in about one week By the tenth day or soon after the contents of the lesions are absorbed and desiccation with crusting and scaling follows

The character and distribution of the skin lesions have diagnostic and prognostic significance In contradistinction to those of chickenpox they are deep within the skin and even in the early stages have a hard "shotty

feel the vesicles are multilocular tough and difficult to break all lesions tend to be at the same stage of development and the distribution of the lesions is peripheral The greatest concentrations are seen on the face forearms wrists palms lower legs and feet including the soles (Fig I 6) The extensor surfaces of the extremities are frequently more heavily involved than the flexor areas Lesions are usually relatively sparse on the chest abdomen and upper thighs

When the skin lesions remain well separated particularly on the face the disease is referred to as discrete smallpox and the fatality rate averages 10 to 15 per cent When the lesions merge or appear to coalesce the disease is spoken of as "confluent" and the mortality rates approach 50 per cent In hemorrhagic smallpox in which there is appreciable hemorrhage into the lesions the fatality rate approximates 80 per cent Purpura variola in which the typical eruption fails to develop is almost invariably fatal (Fig I 7)

Diagnosis The differential diagnosis is concerned particularly with chickenpox and to a much lesser extent with generalized vaccinia Despite the characteristic differences between the eruptions of smallpox and chickenpox either of the alternative diagnoses is hazardous to make in adults particularly in areas where smallpox is known to be endemic Under such circumstances a presumptive diagnosis of smallpox is safer

The variety of useful laboratory aids in diagnosis is perhaps greater for smallpox than for any other virus disease The demonstration of characteristic cytologic lesions was mentioned previously (p 44) as a helpful technique for the confirmation of certain virus infections as well as the detection of virus antigen in lesions These two approaches plus the isolation of the virus and the demonstration of specific antibody response in the patient are all available to confirm a clinical diagnosis of smallpox

In the early macular and papular stages of the eruption smears from



Figure I.6 Smallpox (variola major) characteristic distribution of lesions (Courtesy of Capt. L. D Greentree MC A.U.S.)



Figure I.8 Trachoma characteristic follicles early infection (Courtesy of Dr Phillips Thygeson.)

Epidemiology. The infectivity of the virus is low in the chronic stage but may be high during an acute onset an acute exacerbation or in the presence of secondary infection with bacteria This is particularly true in the case of the gonococcus or *Haemophilus aegyptius* (Koch Weeks bacillus), which are so commonly associated with trachoma in Egypt and the Middle East For the most part transmission requires close personal contact, transfer from mother to child is characteristic Accidental infection of physicians and nurses during surgical procedures has occurred

Pathology. The earliest recognizable pathologic sign of the disease is the cytoplasmic inclusion body, which develops in conjunctival and corneal epithelial cells, it has been demonstrated in the incubation period of the experimental disease in human volunteers The next observable changes are subepithelial infiltration with inflammatory cells particularly plasma cells and the development of lymphoid follicles Follicular hypertrophy, involving principally the tarsal conjunctiva fornix, and upper limbus region is characteristic of the chronic disease Necrotic changes develop slowly but steadily in the subepithelial tissues and result in the conjunctival scars so characteristic of the disease

Clinical Characteristics. Trachoma may start acutely, especially in adults with dense conjunctival infiltration papillary hypertrophy and considerable exudate More often, especially in children the onset is insidious, and there are few external signs other than slight ptosis only when the upper lids are everted are the characteristic follicles of stage I (MacCallan s classification) observed (Fig I 8) The cornea is always involved simultaneously with the conjunctiva but the first epithelial changes consisting of minute fluorescein staining erosions and infiltrates, are recognized only with the biomicroscope The later changes of pannus corneal ulceration and scarring are grossly visible Unlike pannus from other causes, that of trachoma begins in the upper quadrants and is always more extensive there

whose features include lid deformity, corneal opacity and in extreme cases loss of tear function with resultant cornification of the conjunctival and corneal epithelium. Healed trachoma (stage IV) is characterized by a smooth cicatrized conjunctiva and a scarred but noninfiltrated cornea. Mild cases may be symptom free but the complications of trichiasis and secondary infection usually produce persistent irritation.

Diagnosis. The diagnosis of trachoma is ordinarily based on clinical data alone but the finding of cytoplasmic inclusion bodies in scrap



Figure 1.9 Trachoma follicular hypertrophy (Courtesy of Dr Phillips Thygeson)



Figure 1.10 Trachoma late scarring and deformity of lid. (Courtesy of Dr Phillips Thygeson)

ings or of the characteristic microscopic changes (cell necrosis macro *phages) in expressed follicular material may be useful in early and* atypical cases A clinical diagnosis of trachoma may be made when fol licular hypertrophy or scars involving predominantly the conjunctiva of the upper tarsus and fornix occur in association with the characteris tically patterned pannus With the aid of the biomicroscope these diag *nostic changes can be recognized early in the disease*

Acute trachoma at onset must be differentiated from the various types of acute follicular conjunctivitis especially inclusion conjunctivitis (swim ming pool conjunctivitis) and epidemic keratoconjunctivitis For this purpose examination of the cornea is essential since inclusion conjunc tivitis *does not affect the cornea and the keratitis in epidemic keratocon* junctivitis is characterized by coin shaped subepithelial opacities without pannus formation Chronic follicular conjunctivitis is readily differenti able from chronic trachoma on the basis of its lack of pannus formation Severe cicatricial trachoma is occasionally confused with ocular pem phigus or one of the other cicatrizing types of conjunctivitis

Treatment Prior to the introduction of the sulfonamides and the broad spectrum antibiotics treatment was highly unsatisfactory Cures were obtained only rarely The method commonly employed consisted of cauterization of the conjunctiva with chemical agents such as copper sulfate ("blue stone") combined with mechanical expression of the fol licles Sulfonamides and antibiotics have now supplanted cauterizing and surgical procedures and are effective in a high percentage of cases Sul fonamide or antibiotic resistance is rarely encountered The sulfonamides are most effective when administered parenterally the antibiotics when administered topically

Combined antibiotic and sulfonamide therapy is recommended A 1 per cent tetracycline ophthalmic ointment should be applied topically every two or three hours during the day Concurrently one of the less toxic sulfonamides should be administered by mouth in divided dosage suf ficient to maintain a moderate blood concentration (3 to 5 mgm per 100 ml) *of the drug The duration of treatment depends upon the response* of the individual patient

In heavily endemic areas where mass treatment is to be undertaken the antibiotic ointment should be used four times daily for a period of two months Patients found to be resistant on re examination should then receive combined treatment

The prompt combined use of a tetracycline by mouth and Achromycin ophthalmic ointment topically in early cases of trachoma also leads to cure The dosage of Achromycin V for adults is 250 mgm four times daily for four days Children receive proportionately smaller amounts

Prophylaxis There is no specific prophylaxis The problem in en demic areas is essentially the control of the acute ophthalmias This can be accomplished by mass treatment with topical antibiotic preparations The efficacy of such a program however depends upon a network of fixed and mobile ophthalmologic diagnostic and treatment units coordi nated with existing public health facilities

Lymphogranuloma Venereum

Albert B Sabin

Synonyms Climatic bubo tropical bubo Durand Nicolas Favre disease lymphogranuloma inguinale

Definition A specific infectious venereal disease due to a large virus and characterized by transient often unnoticed primary lesions followed by superficial and deep lymphadenitis with eventual suppuration and fistula formation The pelvic colon and rectovaginal septum are frequently involved in the female producing proctitis stricture of the rectum and rectovaginal fistula

Distribution. Lymphogranuloma venereum is widespread throughout the world in both tropical and temperate regions The infection is particularly prevalent among prostitutes and other sexually promiscuous individuals In some areas it is an important public health problem

Etiology The etiologic agent is a large virus (*Miyagawanella lymphogranulomatis*) which may be recovered from the primary genital lesions the affected lymph nodes inflamed tissue of the rectum inflammatory lesions of the colon and the cerebrospinal fluid of patients with meningo encephalitis Large elementary bodies may be demonstrated within the leukocytes in Giemsa Macchiavello or Castaneda stained smears of pus from inguinal buboes There is a striking morphologic resemblance between the elementary bodies of lymphogranuloma venereum and psittacosis These viruses also possess a common antigen

The virus may be propagated by intracerebral inoculation in mice and upon the chorio allantoic membrane or in the yolk sac of the developing chick embryo from which rich suspensions may be obtained These are suitable for preparation of antigen for the Frei skin test and for the complement fixation reaction

Epidemiology Although the disease is transmitted principally by sexual contact accidental laboratory infections indicate that it may be acquired by other routes and without apparent localization or tissue reaction at the portal of entry Cases have been reported in which invasion occurred apparently through the mucous membrane of the upper re

ident fr m sur

The disease is

Pathology The pathology of lymphogranuloma venereum varies with the duration and the severity of the infection The primary lesion which is seldom seen is a transitory small papule vesicle or ulcer From this site invasion of the lymphatics occurs Different routes are followed in the two sexes with resultant differences in the pathologic process and the clinical phenomena In the male the inguinal nodes are involved with further extension to the deep iliac nodes In the female, invasion of the inguinal nodes is uncommon the usual pathologic findings are a pelvic

ings or of the characteristic microscopic changes (cell necrosis macrophages) in expressed follicular material may be useful in early and atypical cases A clinical diagnosis of trachoma may be made when follicular hypertrophy or scars involving predominantly the conjunctiva of the upper tarsus and fornix occur in association with the characteristically patterned pannus With the aid of the biomicroscope these diagnostic changes can be recognized early in the disease

Acute trachoma at onset must be differentiated from the various types of acute follicular conjunctivitis especially inclusion conjunctivitis (swimming pool conjunctivitis) and epidemic keratoconjunctivitis For this purpose examination of the cornea is essential since inclusion conjunctivitis does not affect the cornea and the keratitis in epidemic keratoconjunctivitis is characterized by coin shaped subepithelial opacities without pannus formation Chronic follicular conjunctivitis is readily differentiable from chronic trachoma on the basis of its lack of pannus formation Severe cicatricial trachoma is occasionally confused with ocular pemphigus or one of the other cicatrizing types of conjunctivitis

Treatment Prior to the introduction of the sulfonamides and the broad spectrum antibiotics treatment was highly unsatisfactory Cures were obtained only rarely The method commonly employed consisted of cauterization of the conjunctiva with chemical agents such as copper sulfate ("blue stone") combined with mechanical expression of the follicles Sulfonamides and antibiotics have now supplanted cauterizing and surgical procedures and are effective in a high percentage of cases Sulfonamide or antibiotic resistance is rarely encountered The sulfonamides are most effective when administered parenterally the antibiotics when administered topically

Combined antibiotic and sulfonamide [illegible] per cent tetracycline ophthalmic ointment [illegible] two or three hours during the day [illegible] sulfonamides should be administered by mouth in divided dosage sufficient to maintain a moderate blood concentration (3 to 5 mgm per 100 ml) of the drug The duration of treatment depends upon the response of the individual patient

In heavily endemic areas where mass treatment is to be undertaken the antibiotic ointment should be used four times daily for a period of two months Patients found to be resistant on re examination should then receive combined treatment

The prompt combined use of a tetracycline by mouth and Achromycin ophthalmic ointment topically in early cases of trachoma also leads to cure The dosage of Achromycin V for adults is 250 mgm four times daily for four days Children receive proportionately smaller amounts

Prophylaxis There is no specific prophylaxis The problem in endemic areas is essentially the control of the acute ophthalmias This can be accomplished by mass treatment with topical antibiotic preparations The efficacy of such a program however depends upon a network of fixed and mobile ophthalmologic diagnostic and treatment units coordinated with existing public health facilities

Lymphogranuloma Venereum

Albert B Sabin

Synonyms Climatic bubo tropical bubo Durand Nicolas Favre disease lymphogranuloma inguinale

Definition A specific infectious venereal disease due to a large virus and characterized by transient often unnoticed primary lesions followed by superficial and deep lymphadenitis with eventual suppuration and fistula formation The pelvic colon and rectovaginal septum are frequently involved in the female producing proctitis stricture of the rectum and rectovaginal fistula

Distribution. Lymphogranuloma venereum is widespread throughout the world in both tropical and temperate regions The infection is particularly prevalent among prostitutes and other sexually promiscuous individuals In some areas it is an important public health problem

Etiology The etiologic agent is a large virus (*Miyagawanella lymphogranulomatis*) which may be recovered from the primary genital lesions the affected lymph nodes inflamed tissue of the rectum inflammatory lesions of the colon and the cerebrospinal fluid of patients with meningo encephalitis Large elementary bodies may be demonstrated within the leukocytes in Giemsa Macchiavello or Castaneda stained smears of pus from inguinal buboes There is a striking morphologic resemblance between the elementary bodies of lymphogranuloma venereum and psittacosis These viruses also possess a common antigen

The virus may be propagated by intracerebral inoculation in mice and upon the chorio allantoic membrane or in the yolk sac of the developing chick embryo from which rich suspensions may be obtained These are suitable for preparation of antigen for the Frei skin test and for the complement fixation reaction

Epidemiology Although the disease is transmitted principally by sexual contact accidental laboratory infections indicate that it may be acquired by other routes and without apparent localization or tissue reaction at the portal of entry Cases have been reported in which invasion occurred apparently through the mucous membrane of the upper respiratory tract and through the skin of the hands It is evident from surveys that mild unrecognized infections are not infrequent The disease is especially prevalent in the colored race

Pathology The pathology of lymphogranuloma venereum varies with the duration and the severity of the infection The primary lesion which is seldom seen is a transitory small papule vesicle or ulcer From this site invasion of the lymphatics occurs Different routes are followed in the two sexes with resultant differences in the pathologic process and

lymphadenitis affecting the rectovaginal septum and producing inflammatory lesions of the rectum and rectosigmoid region

Accompanying the acute adenitis in either sex there is inflammation of surrounding tissue with matting of the lymph nodes necrosis and stellate abscesses (which cannot be histologically differentiated from tularemia) and the development of chronic fistulas which may drain for a considerable time Healing is accompanied by extensive scar tissue formation which may lead to elephantiasis of the genitalia and rectal stricture The microscopic picture of the involved lymph nodes and adjacent tissues is that of a subacute or chronic infectious granuloma In the rare instances in which the upper respiratory tract has apparently been the portal of entry there has been involvement of the cervical lymph nodes

Clinical Characteristics The incubation period frequently lasts only a few days The primary lesion may or may not be noticed and usually consists of a small painless papule vesicle or ulcer often disappearing within a week or ten days situated on the penis in the male and commonly on the vaginal wall or cervix in the female

The secondary stage of the disease is characterized by the appearance of lymphadenitis It begins insidiously and runs a chronic indolent course in the male Enlargement of the inguinal nodes of one or both sides is often the presenting symptom At first they are discrete later becoming considerably enlarged matted adherent to the skin and finally fluctuant The overlying skin becomes discolored and ultimately sinus formation occurs with the discharge of a seropurulent exudate which may continue for weeks or months In the female there are often no localizing symptoms prior to invasion of the rectum and the appearance of blood and pus in the stools This stage may be accompanied by constitutional symptoms such as malaise anorexia headache and fever In the rare instances in which infection occurs through the respiratory tract there may be acute disease with chills sweating septic fever and articular rheumatism Severe meningo encephalitis has been reported in a few patients It can occur in individuals who exhibit minimal or negligible evidence of this infection on the genitalia or lymph nodes Untreated it may last for many weeks

The third stage of the disease is most striking in the female It is characterized by chronic proctitis and occasionally by the development of rectovaginal fistula fistulous tracts about the rectum and perirectal abscess The extensive fibrosis often leads to marked rectal stricture In both sexes the disorganization of the lymphatic structures may lead to elephantiasis of the genitalia

Diagnosis In the differential diagnosis the inguinal bubo of lymphogranuloma venereum must be distinguished particularly from that of mild ambulant plague (pestis minor) from syphilis from pyogenic lesions of the lower extremities and from chancroidal infection In plague the affected lymph nodes are much more painful and tender and stained smears of material aspirated from them will reveal *Pasteurella pestis* In the adenitis of syphilis the lymph nodes are discrete not matted or adherent and the primary lesion or its scar is usually demonstrable The bubo occurring in the course of a chancroidal infection should seldom

cause confusion because of the extensive ulceration usually accompanying it The rectal and colonic lesions may be confused with fistulae due to other causes perirectal abscess and chronic infections of the rectum and colon of other types

Meningo encephalitis due to the virus of lymphogranuloma venereum must be differentiated especially from tuberculous or influenzal menin gitis It is the only viral infection of the nervous system which in the early stages is associated with a lowered sugar content in the cerebrospinal fluid Unusually high values for protein (250 mgm to 3570 mgm per 100 ml) are characteristic Pleocytosis may be as high as 4000 leukocytes per cubic millimeter with as many as 75 per cent polymorphonuclear cells during the early stages and it may persist at lower levels with a predominance of mononuclear leukocytes for many months after clinical improvement

The complement fixation test is most useful for diagnosis especially when a fourfold or greater rise in titer can be demonstrated by two suc cessive tests early in the disease A rise may not be demonstrable when the first test is performed more than a month after onset A titer of 1 32 or more in patients exhibiting clinical manifestations compatible with lymphogranuloma venereum may be accepted as confirmatory of the diagnosis except in the presence of early syphilis

The Frei test performed with yolk sac antigen is more specific than formerly and may be positive seven to ten days after onset of adenitis However a positive Frei test may not be noted for five or six weeks The complement fixation test may become positive before the Frei test

Treatment Like other large virus infections of the psittacosis

pected in early cases Later in the presence of extensive damage with fistula formation and fibrosis repeated courses of treatment may be required Enlarged fluctuant lymph nodes should be aspirated but not incised Rectal stenosis and rectovaginal fistula may require surgical intervention

Although the tetracyclines and chloramphenicol are effective during early infection they do not necessarily eradicate the virus and some therapeutic failures occur Therapeutic response to sulfonamides likewise may be incomplete Treatment with either group of drugs must be con tinued for three to six weeks in early cases and for several months in pa tients suffering from chronic disease The recommended dose of tetra

if further treatment is needed the dose should be decreased to 2 grams daily Sufficient fluid must be given to maintain a urinary output of 1500 ml per day to avoid precipitation of sulfonamide within the kidney In adequate antiviral treatment may give rise to resistant strains Combined tetracycline and sulfonamide therapy may prove to be the best treatment

The antimonials are not recommended It is probable that the value ascribed to these preparations in the past has been due to confusion of

diagnosis with granuloma inguinale or chancroid or to an effect on secondary bacterial infection

Infectious Hepatitis

Albert B Sabin Revised by Irving Gordon

Definition Infectious hepatitis (infective hepatitis epidemic jaundice) is an acute diffuse hepatic infection characterized by fever anorexia vomiting abdominal distress and jaundice

Distribution Probably worldwide Although the disease is rarely recognized among the native populations of many tropical and subtropical regions there is evidence that the virus is widely disseminated among them

Etiology and Epidemiology Epidemic hepatitis is presumed to be caused by a virus which is most readily demonstrated in the blood and feces of patients No extrahuman source of the virus is known thus far the infection has been transmitted only to human beings Based on tests

inoculations

Experimental evidence indicates that human feces constitute a source of virus for natural infection and limited explosive water borne milk borne and food borne epidemics have been described The virus is either absent or difficult to demonstrate in the nasopharyngeal washings and urine of patients It is important to note however that the seasonal incidence of large scale epidemics of infectious hepatitis although beginning in midsummer and early autumn frequently does not reach its peak until early or middle winter and ocasionally extends well into spring Epidemics are particularly prone to occur under conditions of poor sanitation and hygiene which favor the dissemination of human fecal material Since the blood is infectious during the incubation period as well as during the early stages of the disease it is probable that inadequately sterilized instruments used in the performance of transfusions blood counts and other procedures may serve as additional means of transmitting the virus

Carriers have been demonstrated who harbored the virus in their feces for as long as a year Gamma globulin prepared from blood obtained from the general population is effective in preventing or ameliorating the disease and thus indicates that the anicteric immunizing infection must be common

Pathology Pathologic changes consist predominantly of an extensive necrosis of the parenchyma associated with an inflammatory response at the periphery of the lobule Liver biopsies performed during the recovery phase of the disease reveal considerable regeneration of hepatic parenchyma and ultimately complete restoration after a period of about two to three months

Clinical Characteristics The incubation period is said to range from ten to 40 days averaging about 25 days The clinical manifestations vary greatly in different individuals and tend to be less severe in children than in adults Mild infections without manifest jaundice are common and it is probable that clinically inapparent infections occur as well

The preicteric phase may vary from one to 21 days the average is about five days Fever chills nausea and vomiting anorexia and epigastric tenderness are the predominating signs and symptoms They may be the only clinical features in nonicteric cases Children are prone to mild anicteric infection and may exhibit little more than brief fever failure to gain weight anorexia change in bowel habit and slight hepatomegaly

The icteric phase may persist from one to ten weeks The average duration is about six weeks The liver becomes enlarged and is usually tender and easily palpable The stools are frequently clay colored Restlessness mental confusion loss of emotional control coma and hemorrhagic phenomena are grave prognostic signs Recovery is gradual convalescence is slow and relapses are common

Death may occur within three to ten days after onset of the illness or as late as the third to the eighth week However the mortality rate is very low Among military patients during World War II the case fatality rate was 1 8 per thousand

Diagnosis Definitive diagnosis is difficult in the preicteric or nonicteric cases since there are no specific laboratory tests for the identification of the virus Bromsulfalein retention is the first liver function test to become positive during the preicteric phase while the serum glutamic oxalacetic transaminase cephalin cholesterol and thymol turbidity tests become positive somewhat later The appearance of bilirubin in increasing amounts in the urine is another diagnostic aid All of these tests may become positive in patients who never develop clinically recognized

to normal

Prophylaxis The prophylaxis against infectious hepatitis entails effective protection against the transmission of human feces or of any material potentially contaminated by it from one individual to another *by food water flies or other indirect means of transfer Because of the* presence of virus in the blood needles and syringes which have been used for patients with the disease should be sterilized by boiling or autoclaving for at least 15 minutes

Normal human gamma globulin in doses of 0 13 ml per kilogram of body weight has been shown to be effective when administered to people exposed to infection in institutional outbreaks Even smaller amounts of

gamma globulin may be effective in preventing hepatitis with jaundice but anicteric disease can be *frequent with lower doses Passive active* immunization probably occurs with resultant prolonged protection

Influenza

Irving Gordon

Synonyms La grippe grip epidemic influenza

Definition Influenza is a specific infectious disease of man usually recognized during epidemics caused by three antigenically distinct influenza viruses The infections they incite cannot be distinguished clinically from one another The disease is characterized by rapid onset of constitutional symptoms and signs and respiratory tract involvement of *varying severity and extent It is usually self limited*

Distribution The disease occurs all over the world and attacks all races all *ages and both sexes It occurs typically in epidemics some* of which are so large that they are almost global and can be termed pandemics During interepidemic periods sporadic cases and sometimes circumscribed outbreaks have been found wherever and whenever a search has been made with laboratory aids

Etiology Influenza is caused by influenza viruses types A B and C All are members of the myxovirus group and are related to newly discovered viruses that have been termed "parainfluenza viruses as well as to mumps virus and certain other viruses (Table 15) The myxovirus group also includes several viruses that cause animal disease and the complement fixing antigen of influenza virus A is present in swine influenza virus and in fowl plague virus The myxoviruses in general and the

via infective droplets Where there is crowding and opportunity for quick spread epidemics are sharp and dissemination rapid The attack rate can be relatively high so that even if the mortality rate is low the disease can be responsible for a great many deaths Carriers have never

mune Most persons experience an infection with one of the influenza viruses *before reaching puberty Infection does not result in long lasting* protection against reinfection which is common Partial immunity is built up however and during numerous exposures antibody develops against a broad spectrum of the influenza viruses Resistance to infection corre

Table 1.5. Myxoviruses that Cause Disease in Man

NAME	COMMON DISEASES
luenza viruses Type A (substrains A1, A2) Type B (substrains B1, B2?) Type C	Influenza, including pneumonitis that is occasionally fatal
umps virus	Mumps parotitis, aseptic meningitis and meningoencephalitis orchitis, pancreatitis etc
ewcastle disease virus	Conjunctivitis (rare)
arainfluenza viruses *	
Type 1 (Sendai virus, Hemadsorption virus I)	Upper respiratory disease, influenza like, pneumonitis of the newborn, often fatal
Type 2 (Croup-associated virus)	Croup and other respiratory infections
Type 3 (Hemadsorption virus II)	Upper respiratory disease

* The term recently proposed for this group of agents is *Myxovirus parainfluenzae* Each member of the group is related antigenically to at least one other member and they share ther properties with mumps and Newcastle disease viruses

ates with the level of the type specific antibody present in the serum Antigenic variation of the influenza viruses can be marked, and this has ed to the use of the symbols A, A1, A2, etc, to distinguish variants After ecovery from an infection from influenza A, there is no resistance to inluenza B, and vice versa

Pathology. The infection is usually confined to the upper respiratory tract but sometimes involves the bronchi or bronchioles, it occasion illy causes pneumonitis Overwhelming viral infection, usually fatal, with viremia and involvement of parenchymatous organs occurs in a few cases during large epidemics, or rarely in sporadic cases Secondary bacterial nfection, often pneumonic, complicates the primary disease The staphylococcus is a particularly dangerous secondary invader

Clinical Characteristics. Influenza A is generally more severe than nfluenza B, although in an individual case it is impossible to differentiate the two diseases At present influenza C is thought usually to be a mild disease

The incubation period of influenza is one to three days It is thought that the symptoms and signs are due to the toxic effect of large amounts of virus produced rapidly in the respiratory tract Onset is sudden with chills or chilliness, fever, headache, malaise, muscular aching and often considerable prostration Nasal discharge, cough or other signs of respiratory involvement are usually not marked, particularly during early acute illness The conjunctivae, however, are often reddened, and there may be photophobia In an uncomplicated case, fever is remittent and lasts for





Figure II 2 *Rickettsia prowazekii* of epidemic typhus in infected yolk cell of chicken embryo showing pleomorphism (filaments short rods and coccoid forms) (Courtesy Rocky Mountain Laboratory photo by N J Kramis)



Figure II 3 *Rickettsia tsutsugamushi* guinea pig tunica cell (Philip C B Scient. Month 69 281 1949)

and visibility under the light microscope They occur as minute coccoid or rod shaped organisms frequently in pairs and sometimes in filamentous forms The electron microscope has shown what appears to be a limiting membrane surrounding a protoplasmic substance containing one or more dense granules

Rickettsiae stain poorly with the ordinary aniline dyes but well by Giemsa's method and most of them especially well with the Macchiavello stain The organism of scrub typhus does not take the Macchiavello stain but stains best by the Giemsa technique When stained by Giemsa's method rickettsiae appear reddish purple, with the Macchiavello technique they stain red, and the cell which contains them appears blue (Figs II 1, II.2, II 3)

The pathogenic rickettsiae have been cultivated only in the presence

Table II.1. Rickettsial Diseases of Man

DISEASE	ETIOLOGIC AGENT	USUAL VECTOR TO MAN	RESERVOIR
Typhus group			
A Epidemic (Brill's disease)	*Rickettsia prowazekii*	*Pediculus humanus humanus*	Man
B Murine	*R typhi*	*Xenopsylla cheopis*	Rat
Spotted fever group			
A American spotted fevers (including spotted fevers of U S A , Canada, Mexico, Panama, Colombia and Brazil)	*R rickettsii*	*Dermacentor andersoni*, *D variabilis* and *Amblyomma americanum* (U S A) *Rhipicephalus sanguineus* (Mexico) *A cajennense* (South America and (?)Mexico)	Ticks, rodents (?), rabbits (?), dog
B Fièvre boutonneuse (including(?)Kenya typhus, South African tick-bite fever, and Indian tick typhus)	*R conorii*	*Rhipicephalus sanguineus* in Mediterranean basin and India *R evertsi*, *A hebraeum*, *Haemaphysalis leachi* in South Africa and Kenya	Ticks, dogs, rodents (?)
C Siberian tick typhus	*R sibirica*	*D silvarum*, *D nuttalli*, *D marginatus*, *D pictus*, *H concinna*, *H punctata*	Ticks, rodents
D North Queensland tick typhus	*R australis*	*Ixodes holocyclus* (?)	Unknown (complement fixation antibodies in rats, bandicoots and other small mammals)
E Rickettsialpox	*R akari*	Mites *Allodermanyssus sanguineus*, *Ornithonyssus bacoti* (?)	House mice (*Mus musculus*)
Scrub typhus (*Tsutsugamushi disease*)	*R tsutsugamushi*	Trombiculid mites *Trombicula akamushi*, *T deliensis* and (?) others	Mites, field rats and mice, and small mammals
Q fever	*Coxiella burnetii*	Infection of man probably by inhalation of contaminated air-borne droplets or dust	Ticks, cattle, sheep, goats, and certain wild animals
Trench fever	*R quintana*	*P humanus humanus*	Man

of living tissue cells The yolk sac of developing chick embryos has proved the most successful medium, except for *Rickettsia quintana* Agar tissue cultures have provided rich growths of the rickettsiae of the spotted fever group Such cultures are convenient for the study of intra nuclear parasitism so characteristic of this group of organisms

The known common reservoir hosts include ticks, mites, small domestic and wild rodents, other small mammals, and some of the larger domestic mammals, for example, cattle, sheep goats and dogs, which are involved in a primary natural cycle in which man occupies a secondary position or intrudes accidentally Man is apparently the reservoir of *Rickettsia prowazekii*, as indicated by evidence that Brill's disease is a recrudes cence of epidemic typhus fever (Table II 1)

While the rickettsiae of epidemic typhus prove fatal to their louse vector, those of murine typhus are not harmful to the flea which man

passed through the eggs from generation to generation

In susceptible experimental animals the rickettsiae accumulate in cells of mesothelial origin especially the lining cells of serous cavities and those of the intima and media of blood vessels The organisms of epidemic murine and scrub typhus and of Q fever are intracytoplasmic in position whereas those of the spotted fever group may appear both in the cytoplasm and in the nucleus

Diagnostic Features of the Rickettsial Diseases

The rickettsial diseases of man have been separated into five distinct groups by virtue of their epidemiologic and immunologic character istics

The definitive diagnosis of rickettsial disease is made by laboratory procedures (1) the serologic reaction of the patient's blood (Table II 2) and (2) the isolation of the specific agent in experimental animals (Table II 3)

The Weil Felix reaction is based upon the production by certain of the pathogenic rickettsiae of nonspecific agglutinins against the "O" *nonmotile variant of certain strains of Proteus* X *The three type* strains in general use for this test are the OX19, OX2 and OXK Living cultures or cultures killed by phenol, formalin or alcohol may be used Twenty *four hour culture suspensions of these organisms, adjusted to a density* of a MacFarland nephelometer reading No 3, are used for the usual *macroscopic* agglutination test with serial dilutions of the patient's serum The tubes are incubated at 37.5° C for two hours are held in the ice box overnight and then read (pp 828–829)

With the exception of Q fever, trench fever and usually rickettsialpox, a rise in Weil Felix titer is characteristic of the rickettsial infections It is important that this rise in antibody titer be demonstrated, and no single titer should be regarded as significant, since Weil Felix titers may sometimes be encountered in sera from persons with illnesses *unrelated* to the rickettsial diseases Louse-borne relapsing fever pro

Table II.2. Rickettsial Diseases—Diagnostic Features in Mar

DISEASE	WEIL-FELIX	SPECIFIC COMPLEMENT FIXATION*	EARLY DISTRIBUTION RASH	PRIMAR ULCER-LOCAL ADENOPA
Typhus group				
A Epidemic (Brill's disease)	OX19	*Rickettsia prowazekii*	Trunk	0
B Murine	OX19	*R typhi*	Trunk	0
Spotted fever group				
A American spotted fevers (including spotted fevers of U S A, Canada Mexico, Panama Colombia and Brazil)	OX19	*R rickettsii*	Extremities	0
B Fièvre boutonneuse (including (?) Kenya typhus, South African tick bite fever and Indian tick typhus)	OX19	*R conorii*	Extremities	+
C Siberian tick typhus	OX19	*R sibirica*	Extremities	+
D Rickettsialpox	Occas OX19	*R akari*	Trunk vari celliform rash	+
E North Queensland tick typhus	OX19 OX2	*R australis*	General	+
Scrub typhus (*Tsutsugamushi disease*)	OXK	*R tsutsu gamushi*	Trunk	+
Trench fever	None	?	Trunk	0
Q fever	None	*C burnetii*	No rash	0

* It is only by the use of washed rickettsial suspensions and by comparison of se titers that specific complement fixation may be observed in the typhus group and in spotted fever group

duces relatively high titers to the OXK strain of *Proteus* organisms i large proportion of cases It is impossible to differentiate epide typhus, murine typhus and Rocky Mountain spotted fever by means the Weil Felix reaction since high OX19 titers may occur in all th diseases When a high OX2 agglutination is obtained it is suggestive an infection with a member of the spotted fever group but an absol diagnosis cannot be made The Weil Felix reaction usually shows a in titer in the late febrile period and in early convalescence but decre in titer in late convalescence Sera from guinea pigs that have b infected with these diseases do not give a Weil Felix reaction, but co plement fixation and agglutination are obtained with rickettsial pensions

OXK is the only strain that is agglutinated in scrub typhus, an rising titer for this strain is considered as diagnostic, provided an fection with louse borne relapsing fever is ruled out

Table II.3. Rickettsial Diseases—Usual Reaction in Laboratory

DISEASE	GUINEA PIG				
	INCUBATION	FEVER	SCROTAL SWELLING	MOOSER CELLS	INTRANUCLEAR RICKETTSIAE
Typhus group	(days)	(days)			
A Epidemic	5–8	6	Rare	None	None
B Murine	3–5	5	Swelling	Usual	None
Spotted fever group					
A American spotted fever (including spotted fevers of U S A, Canada, Mexico, Panama, Colombia, and Brazil) — virulent strain	3–4	5–9	Scrotal necrosis	Endothelial cells with few rickettsiae	Present
— mild strain	4–6	4–5	Rare		Present
B Fièvre boutonneuse (including (?) Kenya typhus, South African tick bite fever, and Indian tick typhus)	3–6	2–4	Swelling	Endothelial cells with few rickettsiae	Present
C Siberian tick typhus	2–6	4–6	Swelling	Endothelial cells with few rickettsiae	Present
D Rickettsialpox	4–6	3–5	Swelling and redness	Endothelial cells with few rickettsiae	Present in tissue culture
E North Queensland tick typhus	4	2–4	Swelling	Endothelial cells with few rickettsiae	Present in tissue culture
Scrub typhus (*Tsutsugamushi disease*)	6–12	5–7	None	None Peritoneal exudate with rickettsiae	None
Q fever	5 7	5–12	None*	None	None

S E = slightly enlarged V L = very large E = enlarged

Trench fever—usual laboratory animals not susceptible

It should be pointed out that this chart represents *usual* reactions with *adapted* strains following *intraperitoneal* inoculation in laboratory animals The period of incubation in original isolations is always longer than is recorded here for adapted strains Likewise [illegible] adapted strains will vary with

Animals Following Intraperitoneal Inoculation (Adapted Strains)

GUINEA PIG				WHITE RAT	WHITE MOUSE
SPLEEN	OUTCOME	IMMUNITY	ORGAN USED FOR PASSAGE		
S [illegible]	Survives	To each other in this group but not to members of other groups	Brain	Inapparent infection cannot be maintained in rats	Same as rat
S [illegible]	Survives		Tunica exudate	Fever scrotal swelling Mooser cells persists in brain	Infection usually survives
E	50-80% mortality	That of A, B and C of this group is complete to each other incomplete or questionable to other members of this group and negative to members of other groups†	Blood	Inapparent infection	Inapparent infection
E	Survives		Blood		
S E	Survives		Tunica exudate	Inapparent infection	Inapparent infection
	Survives	Blood	Inapparent infection	Inapparent infection	
S E	Survives	?	Tunica exudate	?	Infection kills sucklings
S I	Survives		Tunica exudate	?	Inapparent infection
S [illegible]	10–20% mortality	To scrub typhus but not to members of other groups	Brain spleen peritoneal exudate	Same type reaction as guinea pigs persists in brain	85% mortality in 7-21 days peritoneal exudate with rickettsiae
V I	10–20% mortality	To Q fever but not to members of the other groups	Blood or spleen	Mild reaction	Infected usually survives Very large spleen with rickettsiae

the amount of infectious material used for inoculation There is a great variation in strain virulence with different strains and the reactions they induce in the experimental animal will vary

* But a large indurated nonfluctuant lesion develops at site of subcutaneous inoculation with minute amounts of *C burneti*

† However animals vaccinated with A are immune to C but not to B



Figure II 4 Murine typhus Mooser cell Intracytoplasmic rickettsiae in large serosal cell of tunica vaginalis (Courtesy U S A Typhus Commission)

The complement fixation test provides a means for specific diagnosis of epidemic typhus murine typhus the spotted fever group scrub typhus and Q fever For within group differentiation (for example epidemic and murine typhus) it is necessary to use type specific antigens prepared by removing soluble antigens from the rickettsial organisms by repeated washing With the rickettsial suspensions differences between epidemic and murine typhus are often greater in rickettsial agglutination than by complement fixation The soluble antigens are group specific and have been demonstrated for the agents of epidemic
' ' the spotted fever group
ated for the agent of Q
rickettsial agglutination
test likewise has diagnostic value especially in Q fever but for the present large amounts of pure suspension are difficult to obtain

Strains of most of these organisms can be maintained in large male guinea pigs The rickettsiae of scrub typhus are more easily isolated and maintained in mice Certain host reactions in the infected male guinea pig after intraperitoneal inoculation may be useful in differentiating rickettsial diseases These reactions are not invariably obtained and the virulence of the strain for the guinea pig does not necessarily parallel that for man

Characteristically the reactions described in Table II 3 may be observed after inoculation with strains virulent for guinea pigs

1 In Rocky Mountain spotted fever and most other strains of American spotted fever a scrotal swelling which is reducible on pressure and skin necrosis are produced in animals that survive for a sufficient time Later sloughing of the scrotum and necrosis of the skin of the feet and ears may occur The primary pathologic lesion is an endothelial proliferation followed by thrombosis and necrosis In smears of the tunica vaginalis rickettsiae may be seen in both the cytoplasm and the nucleus of large mononuclear cells

2 Murine typhus characteristically produces a nonreducible scrotal swelling with erythema of the scrotum appearing on the first or second day of fever—the Neill Mooser reaction This is essentially an inflammatory reaction of the tunica vaginalis The inflammatory exudate con

sists of large mononuclear (serosal) cells filled with rickettsiae which are intracytoplasmic in position These heavily infected cells are referred to as "Mooser cells" (Fig II.4) In contrast to the characteristic findings in American spotted fever infections, rickettsiae are not found within the nucleus

3 Epidemic typhus and Q fever usually produce no scrotal reaction Certain clinical features of the rickettsial diseases have diagnostic value In scrub typhus, fievre boutonneuse, North Queensland tick typhus and rickettsialpox, there is a characteristic local reaction at the site of inoculation—an ulcer often covered by a black adherent crust (eschar, tâche noir) This is followed by local or regional lymphadenitis

The characteristic initial distribution of the rash is likewise helpful in differential diagnosis In epidemic typhus, murine typhus, scrub typhus and trench fever, the rash appears first on the trunk and later spreads to the extremities In diseases of the spotted fever group the rash appears first on the extremities, ankles and wrists, and may then spread over the entire body, except the palms and soles In Rocky Mountain spotted fever the rash usually appears first on the wrists and ankles and spreads later to the trunk, palms and soles The rash in rickettsialpox is characteristic and resembles that seen in chickenpox The individual lesions of this rash begin as small erythematous papules which, as they increase in size, acquire a centrally located vesicle

Prophylaxis. Rickettsioses are controlled (1) by preventive measures against the source of infection, and (2) by vaccination of exposed personnel Control practices depend upon the epidemiologic background of the specific disease However, in general, they include sanitary measures, insecticides directed against arthropod vectors, extermination of animal "reservoirs" such as rats and other rodents, destruction of rat harborages, use of protective clothing and insect repellents, and environmental sanitation to reduce exposure to contaminated animal and arthropod fomites

Practical vaccines against epidemic typhus and Rocky Mountain spotted fevers have been developed commercially using yolk sacs of infected chicken embryos as sources of antigen Attempts at producing vaccines against other rickettsioses have had varied results, for example, vaccines against murine or endemic typhus and scrub typhus Still under development are vaccines against Q fever Others have not been attempted or are not needed

Treatment. All the pathogenic rickettsiae are susceptible to the broad spectrum antibiotics, chloramphenicol and the tetracyclines (Achromycin, Aureomycin and Terramycin), and regimens for therapy are provided under the individual rickettsioses

6

Epidemic Typhus

John P. Fox

Synonyms Jail fever, ship fever, typhus exanthematicus, louse typhus, Fleckfieber (German), typhus exanthématique (French), tabardillo (Spanish).

Definition An acute infectious disease caused by *Rickettsia prowazekii* transmitted by the body louse *P. humanus humanus*. It is characterized by fairly abrupt onset, continuous fever of about two weeks' duration accompanied by severe headache and marked prostration, a characteristic rash appearing about the fifth day, first in the axillae, on the loins, abdomen and back, which frequently becomes petechial, and terminating by crisis or rapid lysis. Case fatality in untreated patients rises sharply with age and in middle age and over usually exceeds 50 per cent.

Distribution Typhus fever in the epidemic form has appeared in all continents except Australia. It is prevalent chiefly in cooler areas, including the higher altitudes of the tropic zone, especially where heavier clothing is worn and change of clothing is infrequent. It was a disease of ancient times when it was frequently confounded with typhoid and plague. The great epidemic center has been Europe. During and following World War I extensive epidemics appeared in Poland, Russia, Serbia and Rumania. In parts of Europe, especially in Poland and Rumania, and during the Italian campaign in Ethiopia, typhus was accompanied by relapsing fever. Later epidemics occurred in Morocco, Algiers, Tunis, Italy and Egypt. It has also been prevalent at times in several areas in southern Africa (Fig. II 5).

In Asia the northern part of the continent and the mountainous area toward the south are chiefly affected. In the Americas the mountainous areas of Mexico, Central America and western South America have experienced *small to major outbreaks in modern times. Recent studies in* Peru indicate that in the Andean Indian population overt disease and subclinical infections occur in endemic fashion resulting in immunity in

... per cent above age 40). In the

... as not occurred in recent times

... ase) occur occasionally in im...

... endemic areas.

Etiology *Rickettsia prowazekii* is one of the larger rickettsiae ... stains by both Giemsa and Macchiavello methods and cannot be differ-

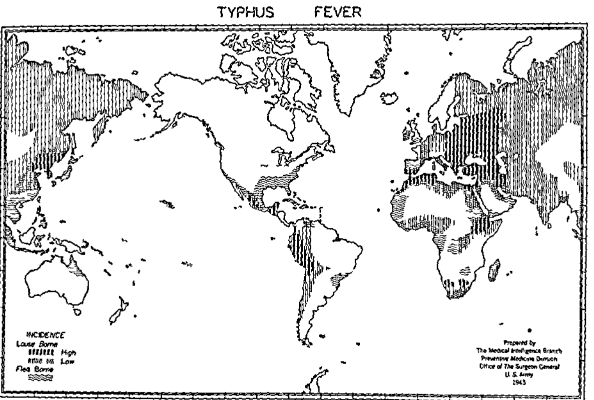


Figure II 5 Geographic distribution of epidemic and murine typhus

6

Epidemic Typhus

John P Fox

Synonyms Jail fever ship fever typhus exanthematicus louse typhus Fleckfieber (German) typhus exanthematique (French) tabardillo (Spanish)

Definition An acute infectious disease caused by *Rickettsia prowazeki* transmitted by the body louse *P humanus humanus* It is characterized by fairly abrupt onset continuous fever of about two weeks duration accompanied by severe headache and marked prostration a characteristic rash appearing about the fifth day first in the axillae on the loins abdomen and back which frequently becomes *petechial and terminating by crisis or rapid lysis Case fatality in un*treated patients rises sharply with age and in middle age and over usually exceeds 50 per cent

Distribution Typhus fever in the epidemic form has appeared in all continents except Australia It is prevalent chiefly in cooler areas including the higher altitudes of the tropic zone especially where heavier clothing is worn and change of clothing is infrequent It was a disease of ancient times when it was frequently confounded with typhoid and plague The great epidemic center has been Europe During and following World War I extensive epidemics appeared in Poland Russia Serbia and Rumania In parts of Europe especially in Poland and Rumania and during the Italian campaign *in Ethiopia typhus was accompanied by* relapsing fever Later epidemics occurred in Morocco Algiers Tunis Italy and Egypt It has also been prevalent at times in several areas in southern Africa (Fig II 5)

In Asia the northern part of the continent and the mountainous area toward the south are chiefly affected In the Americas the mountainous areas of Mexico Central America and western South America have experienced small to major outbreaks in modern times Recent studies in Peru indicate that in the Andean Indian population overt disease and subclinical infections occur in endemic fashion resulting in immunity in a high proportion of the population (90 per cent above age 40) In the United States and Canada transmission has not occurred in recent times although recrudescent cases (Brill s disease) occur occasionally in immigrants from Central Europe and other endemic areas

Etiology *Rickettsia prowazekii* is one of the larger rickettsiae stains by both Giemsa and Macchiavello methods and cannot be differ

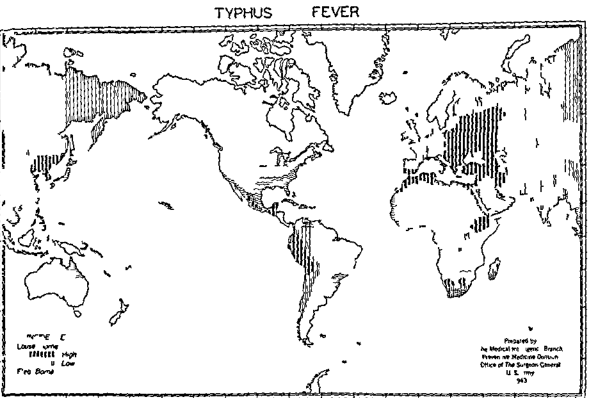


Figure II 5 Geog aphic dis ribu on of ep demic and murine typhus

becomes afebrile Presumably because they are antagonistic to para aminobenzoic acid (PABA is naturally present in the body and in large doses is itself a potent chemotherapeutic agent) sulfonamides are *contraindicated* in epidemic typhus and other rickettsial infections

Prophylaxis All persons entering a typhus area should be im munized with an effective vaccine made from killed *R prowazeki* The Cox type yolk sac vaccine was extensively used during World War II Although it did not completely prevent infection among exposed personnel the course of the disease among vaccinated individuals was much shorter and milder the incidence of serious complications greatly reduced and the mortality practically nil It is recommended that two doses each of 1 ml be given subcutaneously at intervals of ten to 14 days This should be followed by a booster dose of 1 ml after six to nine months and subsequent boosters at yearly intervals Since this vaccine contains egg protein sensitivity must be watched for and the vaccine must be administered with caution to egg sensitive individuals

It must be remembered that whereas a clinical attack of epidemic typhus confers protection against murine typhus immunization with the killed rickettsiae of epidemic typhus does not produce such cross immunity

Although not commercially available at the moment vaccine contain ing a living attenuated strain of *R prowazeki* (strain E) has been under evaluation since 1951 A single intramuscular inoculum of proper dosage (between four and five log egg infective doses) induces with a tolerable level of reaction solid immunity to later virulent challenge This immunity has been observed to endure for at least five and a half years It also induces lesser but significant resistance to virulent murine typhus challenge

The mass protection of population groups in the presence of epi demic typhus involves the extensive application of delousing measures with adequate ... ibers of the community anc ... iduals into treated areas ... cases is of the utmost urgency in the control of an epidemic This in turn entails an effective case finding and reporting mechanism

Mass disinfestation is easily and rapidly accomplished by the use of louse powders blown into each individual s clothing by hand or power dusters DDT 10 per cent in an inert base such as talc or pyrophyllite has proved most effective and the lethal effect on lice persists for more than two weeks When a DDT resistant strain of lice is encountered as was the case in Korea lindane 1 per cent in inert dust should be sub stituted Three applications are desirable at seven day intervals each not to exceed 60 grams of lindane per person (Table XI 10 p 772)

Medical and control personnel working in an epidemic area must exercise great care to avoid infection Lousy clothing should be removed and sterilized and the patient himself should be thoroughly deloused Attendants should wear clothing impregnated with a lousicide and in view of the infectiousness of dried louse feces they should wear pro tective masks goggles and gloves while they are in a potentially in fected environment

Important subsidiary measures include improvement of living conditions provision for adequate bathing and laundering facilities and the dispensing of additional supplies of clothing and food

Brill s Disease

Brill s disease formerly confused with murine typhus in the southern United States is now recognized as first suggested by Zinsser, as a recrudescence of infection with *R prowazeki* Although unusually rapid and high level antibody response, probably related to prior experience with the rickettsial antigen may be suggestive the diagnosis may be

es the

s that

prin

cipally in persons who have emigrated from Central Europe many of whom have had recognized epidemic typhus many years before In Central Europe probable cases are being recognized with increasing frequency For example 26 cases were reported from Yugoslavia in the summer of 1950 of whom 21 gave a history of typhus five to 12 years previously Proof of Zinsser s hypothesis has been established by serologic studies and by recovery of *R prowazeki* both from patients with Brill s disease and in two instances from lymph node material obtained by biopsy from healthy persons known to have had typhus several years previously Although experimental Brill s disease has been induced in monkeys recovered from prior infection by the inoculation of cortisone the factors that provoke recrudescence in man remain to be defined Epidemiologically the phenomenon of long enduring latent infection with recrudescence and renewed infectivity for lice constitutes an important reservoir mechanism for *R prowazeki*

7

Murine Typhus

John P Fox

Synonyms Endemic typhus flea typhus Brill s disease (incorrect usage southern U S A)

Definition. An often serious febrile disease of about fourteen days duration caused by *Rickettsia typhi* and transmitted by flea bites or by contact with flea feces

Distribution Murine typhus is worldwide in distribution in areas of warmer climates (Fig II 5)

Etiology *Rickettsia typhi* is indistinguishable from *R prowazekii* morphologically, is closely related to it in antigenic character and shares with it many other properties The host range of *R typhi* is broader and includes domestic rats and possibly other rodents in nature and the mouse in the laboratory Infection of male guinea pigs characteristically results in marked scrotal swelling which is associated with the finding of large masses of rickettsiae in the cytoplasm of the serosal cells of the tunica vaginalis (Neill Mooser reaction) Experimental infection of the human body louse *P humanus humanus* also is easily accomplished

Epidemiology Although various rodents including the eastern cotton rat (*Sigmodon hispidus*) are readily infectible in the laboratory and possibly may play a role in nature the only clearly demonstrated natural role is that played by commensal rats especially *Rattus norvegicus* Acute infection of the rat results in [illegible]
ricketts[illegible]
are [illegible]
seve[illegible] has not been observed so far hence the individual rat probably is a source of infection only once and then only briefly Various rat ectoparasites become infected and are presumed to help spread infection from rat to rat These include the mite *Ornithonyssus bacoti* the rat louse *Polyplax spinulosus* and the fleas *Nosopsyllus fasciatus* (more common in temperate zones and rarely feeding on man) and *Xenopsylla cheopis* (the tropical rat flea) This latter is considered the most important vector both from rat to rat and from rat to man and the summer and fall seasonal peaks of murine typhus in man closely parallel similar variations in abundance of these fleas Undisturbed by the infection the flea remains infectious for its entire remaining life span Transovarial passage of infection fortunately does not occur Human infection probably takes place chiefly by rubbing flea feces into the skin while scratching but may also follow inhalation of dry flea feces

Disease occurrence in man is largely influenced by season (see above) and by occupational exposure (food warehouses granaries poultry farms) The latter factor explains why in the southern United States the incidence in men is twice that in women In the United States recognized murine typhus reached its peak in 1944 and 1945 with 5401 and 5193 reported cases respectively plus an estimated 20 000 unreported cases each year Since then there has been a steady and abrupt decline despite intensified efforts at case finding Only 114 cases were reported in 1957

Spread of *R typhi* from man to man via the human body louse has been reported on the basis of inadequate evidence for example testing strains isolated for ability to induce scrotal reactions in guinea pigs rather than for antigenic character However the laboratory demonstrated infectibility of the body louse supports the possibility of this mechanism being important in areas (Mexico and China) where human louse infestation and *R typhi* may coexist

Pathology. The pathologic findings in murine typhus in general are similar to those in epidemic typhus However, they are not known in detail since fatalities are uncommon (less than 5 per cent in the U S A) It is probable that histopathologic changes in the small vessels similar to the alterations seen in epidemic typhus occur Cutaneous petechiae are infrequent, and large areas of skin necrosis have not been reported

Clinical Characteristics. Except in persons over 50, murine typhus is in general a milder disease than the epidemic variety The onset follows an incubation period of six to 14 days and may be either abrupt or gradual In the latter case the temperature rises to 102° to 105° F during the first week and remains elevated until about two weeks after onset The rash, usually limited to the chest, abdomen and inner surfaces of the arms, resembles that of epidemic typhus, except that petechiae are rare The macules, appearing about the fifth day, at first fade on pressure but soon lose this characteristic After two to ten days they disappear The temperature usually falls by rapid lysis and recovery is complete, although convalescence may be delayed Mental symptoms are not marked and complications are rare

Diagnosis. The diagnosis of murine typhus presents problems similar to those of epidemic typhus The serologic procedures described for epidemic typhus, including the Weil-Felix test, are equally applicable as are the methods for agent isolation and identification (pp 828–829) In the male guinea pig, in addition, there may be the characteristic development of scrotal swelling (without the necrosis seen with Rocky Mountain spotted fever) and the demonstration of Neill-Mooser bodies (aggregates of rickettsiae) in smear preparations of serosal cells of the tunica vaginalis Isolation also may be accomplished by direct inoculation of sterile ground blood clot into the yolk sacs of seven day chick embryos

Treatment and Prophylaxis. The treatment of murine typhus is the same as that for epidemic typhus

Since rats constitute the primary reservoir in nature, poisoning, trap ping and rat proofing are logical procedures for control Rat proofing is the only measure of permanent value Particular attention should be paid to granaries and storehouses thereby depriving rats of their major food supply

The control of fleas by the use of DDT in dusting rat runs is con sidered by most workers to be the best modern method of controlling murine typhus

A practical vaccine against murine typhus has not been perfected

8

American Spotted Fevers

E J Bell Revised by C B Philip

Synonyms Rocky Mountain spotted fever exanthematic typhus of Sao Paulo Tobia fever Choix fever pinta fever

Definition An acute febrile disease caused by *Rickettsia rickettsii* (Fig II 10) and transmitted by the bite of certain ticks It is characterized by a rash that appears first on the wrists and ankles and later in some cases over the entire body including the face the palms of the hands and soles of the feet

Distribution Formerly thought to be restricted to certain areas of the Rocky Mountain states the disease has since been reported from British Columbia Alberta and Saskatchewan (Canada) from 45 states (U S A) and from Brazil Colombia Mexico and Panama In Brazil the disease was originally reported as exanthematic typhus of Sao Paulo and in Colombia as Tobia fever Choix fever or pinta fever in northern Mexico has also been identified with spotted fever

Etiology *Rickettsia (Dermacentroxenus) rickettsii* has the general characteristics of *R prowazekii* without filamentous forms and in addition is capable of invading the cell nucleus The spotted fever diseases of the United States Canada and the various Latin American countries represent a single disease entity as indicated by specific serologic tests or other laboratory studies

Epidemiology Spotted fever is essentially a rural disease occurring in areas where ticks and their rodent hosts are prevalent However in the eastern United States the tick vector is frequently brought into yards by dogs and foci of infection have thus been established in some suburban areas Since the tick is not an habitual parasite of man the disease does not as a rule appear in epidemics but in some heavily tick infested areas in Colombia it has reached almost epidemic proportions and in other areas multiple infections in the same family are not as infrequent as they were once thought to be

The *severity of the disease may vary greatly in areas* separated by only short distances The degree of virulence within each of these areas appears to be relatively constant although unexplained

Tick vectors may be considered in two groups (1) ticks which feed

both on wild rodents and on man, and (2) ticks which serve as vectors among wild rodents but do not feed on man or seldom come in contact with him Ticks are believed to furnish the chief reservoir mechanism in nature, since the organisms have not been observed to survive longer than a month in small animal tissues However, recovery of a strain was recently reported from lymph nodes of a man convalescent one year

(1) The common vectors of the human disease are in western Canada and the western United States, the wood tick, *Dermacentor andersoni* Stiles, in the eastern United States, the dog tick, *D variabilis* (Say), and in Texas and Oklahoma, the Lone Star tick, *Amblyomma americanum* (Linn) As a rule only the adults of the two species of *Dermacentor* feed on man, nymphs, however, may in rare instances feed on children On the other hand, larvae, nymphs and adults of *A americanum* have been found on man In Mexico, *Rhipicephalus sanguineus* (Latr) is the only proved vector to man, but *A cajennense* (Fabr) has also been found naturally infected there In Colombia and Brazil *A cajennense* is the accepted vector, and all active stages likewise attack man Several other species of ixodid ticks and at least three species of argasid or soft ticks are efficient experimental vectors (see p 679)

(2) The rabbit tick *Haemaphysalis leporis palustris* (Packard), an important vector of *Pasteurella tularensis* among rabbits, is also considered an important vector of spotted fever among these animals It is found over most of the United States and in southern Canada This tick

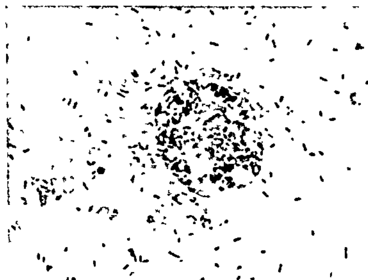


Figure II 10 *Rickettsia rickettsii* causative agent of Rocky Mountain spotted fever in stained smear of infected yolk sac of chicken embryo Extracellular and intracellular bodies and possibly some intranuclear (see halos around some organisms) are depicted. (Courtesy Rocky Mountain Laboratory photo by N J Kramis.)



Figure II 11 Rocky Mountain Spotted fever lesion of skin showing thrombosis necrosis of vessel wall and perivascular infiltration

does not feed on man Rabbits however are hosts also to *D andersoni* a common vector to man The argasid tick *Ornithodoros parkeri* Cooley may play an equally important role in nature in nine western states It has several hosts in common with *D andersoni* and transmission through the egg to the fourth generation with no reduction in the virulence of the rickettsiae over a period of five years has been demonstrated This tick feeds readily on man but seldom comes in contact with him Field mice and dogs common hosts of the immature and adult stages of *D variabilis* respectively appear to be important vertebrates involved in the chain of transmission of *R rickettsii* in nature in parts of the eastern United States

The infection is commonly transmitted to man by the bite of the infected tick Occasional instances of infection have occurred however following contamination of the hands by crushing ticks while removing them from domestic animals

Pathology The pathologic findings in Rocky Mountain spotted [illegible] ound in small [illegible] n the histopathologic findings and in the structures affected In Rocky Mountain spotted fever there is greater destruction of the deeper layers of the vessel walls and less perivascular infiltration The rickettsiae invade both the vascular endothelium and smooth muscle fibers of the vessel wall causing endothelial proliferation necrosis of the wall thrombosis and infarction with hemorrhage into the surrounding tissues These lesions occur predominantly in the skin and subcutaneous tissues the voluntary muscles and the testes with resulting areas of necrosis There are no distinctive changes in the viscera the spleen is commonly much en

larged firm and dark red in color Lesions of the central nervous system are uncommon (Fig II 11)

In fatal cases the rash is hemorrhagic and necrosis of the scrotum or vulva is frequent There may likewise be necrosis of the prepuce, fingers toes lobes of the ears or of the soft palate Hemorrhages into the muscles and subcutaneous tissues are widespread with frequent confluence of the rash at points of bed pressure such as the buttocks

Clinical Characteristics Both mild and virulent strains of Rocky Mountain spotted fever are well known, and contrary to former belief both are found in all regions where the disease occurs Depending on the virulence of the strain the incubation period varies from three to 14 days. In the severe type the onset is sudden with headache chills marked pains in the joints and generalized body pains The fever rises gradually or fairly rapidly to about 104° F and remains elevated without morning remissions On the third or fourth day the rash makes its appearance At first it closely resembles that of measles but unlike the latter exanthem it remains discrete in its subsequent course The eruption begins as macules on the forearms and ankles later spreading inward along the extremities to the trunk and forehead (Fig II 12) There is a still later spread to the palms soles and scalp when mucous membranes may also be involved The mature lesions frequently become petechial There is a moderate leukocytosis and the differential count is not characteristic

The height of the illness is reached in the second week At this time the pulse becomes rapid and weak and nervous symptoms especially delirium may appear It is during this period that necrosis and death occur If the patient survives the 14th day his chances for recovery are excellent

The temperature shows a gradual fall during the third week Areas

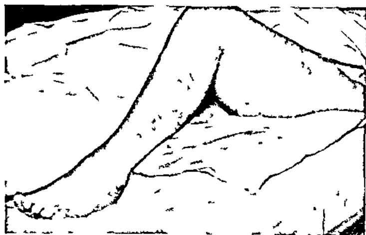


Figure II 12. Generalized rash of Rocky Mountain spotted fever (Courtesy U S P H S Rocky Mountain Laboratory)

in which the rash was most petechial often show scaly exfoliation or occasionally castlike desquamation There may be residual cicatrices in such areas of the skin Complications such as deafness and visual disturbances may follow severe attacks but are not permanent Convalescence is rapid in uncomplicated cases

The mortality depends on the virulence of the rickettsial strain and on the age of the patient Fatality rates as high as 80 per cent are known for some strains others do not exceed 5 per cent Persons over 50 years of age are particularly prone to die of Rocky Mountain spotted fever whereas children are but slightly affected as a rule The overall case fatality rate from this disease in the United States was previously about 19 per cent but has recently become practically nil with the introduction of the newer antibiotics into the treatment of the disease

Diagnosis *A history of recent contact with ticks especially in regions where the prevalence of this disease is recognized* should direct suspicion toward a diagnosis of Rocky Mountain spotted fever In the absence of such evidence the physician must rely principally upon laboratory tests The initial distribution of the rash on wrists and ankles is suggestive but the clinical distinction between Rocky Mountain spotted

it is posi

Mountain

X2 is like-

wise only partially helpful since some cases of typhus give a similar reaction Complement fixation becomes positive during the second week This test is highly specific in differentiating Rocky Mountain spotted fever from both epidemic and murine typhus In both the above serologic tests it is the *rise* in titer of the second and subsequent blood samples that is of significance There is accumulating evidence that specific therapy with antibiotics often inhibits the formation of complement fixing antibodies while not appreciably affecting the results of the Weil Felix test

Since the rickettsiae are present in the blood of man throughout the febrile course of the disease intraperitoneal inoculation of male guinea pigs with ground up clot of the patient s blood may have diagnostic value Strains of rickettsiae virulent for guinea pigs typically produce a characteristic scrotal necrosis mild strains however often do not The rickettsiae in cells of the tunica vaginalis exudate may be intranuclear as well as intracytoplasmic in position an important diagnostic point

The severity of the infection for man bears no relation to the intensity

is

nd

ly

virulent for the guinea pig

Treatment The broad spectrum antibiotics chloramphenicol and the tetracyclines (Achromycin Aureomycin and Terramycin) have all proved highly effective in the treatment of Rocky Mountain spotted

fever With each of these drugs clinical manifestations of the illness have been arrested in about two to three days

Therapeutic regimens are similar for each of the drugs the general schedule used satisfactorily at present is as follows An initial dose for adults of about 3 to 4 grams is given orally, and this is followed by a similar amount daily in divided doses until the temperature returns to normal With Aureomycin and Chloromycetin the daily schedules have generally consisted of 0 25 gram doses every two or three hours whereas with Terramycin and Achromycin 1 0 gram every eight hours has proved satisfactory

Sole reliance upon the antibiotic in seriously ill patients late in the course of their disease is inadequate Treatment utilizing transfusions of saline glucose plasma and whole blood is vital for support of the embarrassed circulatory system Febrile and toxic manifestations are ameliorated by supplemental cortisone 200 mgm initially and two further doses of 100 mgm at six hour intervals Two thirds of this amount is recommended for antitoxic measures in children

Prophylaxis In areas where Rocky Mountain spotted fever commonly occurs it has been found practicable to immunize large groups of the population by the inoculation of a killed suspension of the specific rickettsiae Such vaccination reduces the incidence and also lessens the severity of those attacks which may subsequently occur The injections should be repeated yearly in those likely to be exposed

Tick infested areas should be avoided if possible if not clothing treated with repellent such as diethyl toluomide should be worn (see Table XI 10 p 778) Careful inspection of the body surface should be made every few hours to remove any ticks that may have entered the clothing Infected wood ticks may inoculate an individual within six hours after attachment hence regular removal of ticks is an important measure in avoiding infection

Numerous insecticides are effective in providing temporary control in localized areas and on vegetation along roadsides pathways and other places where ticks concentrate (see Table XI 10 p 776)

Ticks should be removed from dogs with forceps or a piece of paper rather than by grasping them between the unprotected fingers The hands should be washed with soap and water after contact with ticks

9

Related Spotted Fevers and Rickettsioses

C B Philip

Fievre Boutonneuse

Synonyms. Boutonneuse fever, *fievre exanthematique de Marseille escarro nodulaire* (French)

Definition. A disease of the spotted fever group caused by *Rickettsia conorii* which is transmitted in the Mediterranean area and probably in India chiefly by the tick *Rhipicephalus sanguineus* (Latr) A "tâche noir" is present The rash appears on the trunk and may subsequently *involve the entire body*

Distribution. First reported from Tunis in 1910 fievre boutonneuse is now known to be endemic in most countries of the Mediterranean Basin and in the Crimea Similar infections reported in South Africa, Kenya Ethiopia, the Belgian Congo and certain other places in Africa have been considered to be the same disease, but recent observations have again cast doubt on their complete identity with the Mediterranean agent Present evidence from specific serologic and other laboratory investiga*tions suggests that a similar rickettsiosis occurring in the Northwestern* Frontier Province and Kumaon Hills of India is identical with fievre boutonneuse

Etiology. *Rickettsia* (*Dermacentroxenus*) *conorii* is the etiologic agent Intranuclear rickettsiae have been reported, but the organisms are much less regularly seen in this position than are the rickettsiae of the [illegible] proves

[illegible] stic dog

[illegible] pidemi

[illegible] volved

is therefore comparable to that of spotted fever in the [illegible] United States, where dogs are prominent hosts of the adult tick vector In Kenya *Rhipicephalus simus* (Koch) and *Haemaphysalis leachi* (Audouin) are also reported as vectors in addition to *R sanguineus* so that cases are [illegible] as well as on the premises

[illegible] *ly as varied an epidemiology* as [illegible] infections are contracted more

often in the fields or veld than in urban areas The larvae of *Rhipicephalus evertsi* (Neumann) and *Amblyomma hebraeum* (Koch) are the common vectors in certain rural areas while the dog tick *H leachi* seems to play an important role in the dissemination of the infection into the suburbs This latter tick in which hereditary transmission of the agent has been demonstrated constitutes a natural reservoir of this rickettsia

From R *sanguineus* ticks caught on the premises of a former tick

Pathology Detailed pathologic findings in fievre boutonneuse Kenya typhus and South African tick bite fever have not been reported because of the low mortality

Fievre boutonneuse South African tick bite fever and Kenya typhus differ from the spotted fever of the Americas in the frequent occurrence of a primary lesion (tache noir) supposedly at the site of the infective

equently ulcerates and

rash of fievre boutonneuse is said to reveal swelling of the vascular endothelium with perivascular infiltration purpuric le

Clinical Characteristics

alike from the clinical point of

have been noted After an incubation period of about a week there is usually an abrupt onset with chills and a rapid rise of temperature to about 104° F At this time the primary ulcer is already present Except for persistent insomnia headache and muscular pains the febrile course is accompanied by less extreme symptoms than in the other rickettsial diseases Prostration and delirium are not marked The fever usually lasts one to two weeks and the temperature then drops rapidly to normal The mortality is low

On the second to fourth day the rash appears on the trunk and extremities It is macular or maculopapular and may become hemorrhagic but not coalescent The palms soles and face are involved later the abdomen however may show few lesions

Diagnosis Clinical diagnosis of these three diseases is simplified by a history of tick bite The discovery of a tâche noir and its associated regional lymphadenopathy is of great diagnostic significance The rash

complement fixation test is positive for the spotted fever group

Guinea pig inoculations result in nonfatal typhus like reactions which vary in intensity and regularity according to the particular strain of the rickettsia injected In this animal fièvre boutonneuse cannot be distinguished from other spotted fever strains of low virulence except possibly by cross vaccination or refined complement fixation tests It cross immunizes with Rocky Mountain spotted fever strains of both high and low virulence and with tick bite fever of South Africa However Rocky Mountain spotted fever vaccine which affords complete protection

against the homologous disease in guinea pigs, gives no protection against fièvre boutonneuse

Treatment. Treatment is the same as described for American spotted fevers As in other typhus like illnesses, good nursing care is important Palliative measures and sedation are indicated in the more severe cases

Prophylaxis. *Ticks and tick-infested areas should be avoided when* possible Since dogs are the usual hosts of several of the vector ticks of fièvre boutonneuse and related diseases, special care should be exercised in preventing tick infestation of such pets and of human habitations Effective tick repellents and insecticides for such purposes are available A short haired dog might be considered a more desirable domestic animal in endemic areas Strays or wild dogs should be exterminated The preventive measures advocated for Rocky Mountain spotted fever apply also in the prevention of this disease Immunizing vaccines have been reported only for the American spotted fevers, but vaccines against these rickettsial agents do not confer protection against fièvre boutonneuse

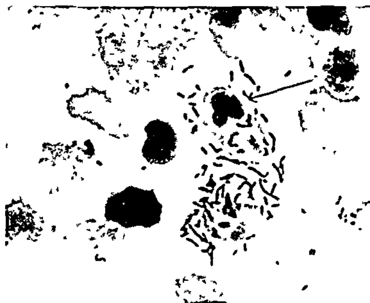


Figure II 13 *Rickettsia siberica* causative agent of Siberian tick typhus showing clump of organisms inside nucleus and scattered in cytoplasm of cells from scrotal sac of infected guinea pig (Courtesy of P F Zdrodovskiy)

Siberian Tick Typhus

A tick-borne rickettsial disease of the spotted fever group has been reported from eastern and central Siberia (Fig II 13) The illness is mild and is characterized by the occurrence of a lesion at the site of the tick bite, regional lymphadenitis, headache and rash *Dermacentor nuttalli* (Olenev), *D silvarum* (Olenev), *D pictus* (Herm), *Haemaphysalis concinna* (Koch) and *H punctata* (Can and Fanz) are the reported

vectors Natural infection with the causative rickettsia and its trans
tick species Clini
boutonneuse, but
ver with its natural
cycle between native rodents and their immature tick parasites Man is bitten accidentally in grassy meadows and steppes and brushy hillsides by the adults The Weil Felix and complement fixation tests are positive for the spotted fever group but cross vaccination in guinea pigs suggests closer relationship to spotted fever than to fievre boutonneuse

10

Rickettsialpox

C B Philip

Synonym Kew Gardens spotted fever

Definition Rickettsialpox is a relatively mild to moderately severe nonfatal typhus like disease accompanied by a varicelliform rash lymphadenopathy and leukopenia It is preceded by an initial lesion or eschar at the portal of entry at the site of attachment of a mite

Distribution Proved cases have been restricted to certain urban communities on the North Atlantic seaboard of the United States and to certain cities in the U S S R Under the name "rickettsiose vesiculeuse" the disease has been reported but not confirmed in French Equatorial Africa

Etiology The intracytoplasmic agent *Rickettsia (Dermacentroxenus) akari* is capable of invading the nucleus of infected host cells (Fig II 14) Cross reactions in the complement fixation tests indicate a relationship to the spotted fever group of tick borne rickettsiae In addition to man wild and laboratory mice guinea pigs and chick embryos but not monkeys have been shown to be susceptible

Epidemiology Proved cases have been resident in house mouse infested dwellings in urban areas including modern apartment developments In some instances outbreaks have approached epidemic proportions The epidemiology in the U S S R is almost identical to that in the U S A including laboratory behavior of isolates of the agent (named *R (D) murina* in the former country)

The natural vector is a widespread though not common mite parasite of mice *Allodermanyssus sanguineus* (Fig XI 4 p 683) However the more ubiquitous tropical rat mite *Ornithonyssus bacoti* can transmit the disease experimentally Natural infection has been demonstrated in mice (as well as in commensal rats in the U S S R) and in *A sanguineus* Unlike trombiculid vectors of scrub typhus which are parasitic in the larval



Figure II 14 *Rickettsia akari*, the agent of rickettsialpox in a cell from the peritoneum of an infected white mouse (Courtesy Rocky Mountain Laboratory photo by N J Kramis)

stage only, these mites are hematophagous in all active stages and usually leave the host between blood meals

Patients are not aware of attachment of the rapidly feeding mites and are probably attacked while asleep Prevalence of the disease according to age, sex and occupation is proportionate to these characteristics in the residents of the endemic loci Ages of patients have ranged from less than one year to over 50 years

Pathology. Reports of pathologic findings in humans are confined to biopsy studies of the histopathology of primary and secondary cutaneous lesions During the fastigium of the disease the initial lesion at the site of attachment of the infected mite consists of a shallow ulcer approximately 0 5 cm to 1 5 cm in diameter It is covered with a brown to black crust and is surrounded by an erythematous area about 2 5 cm in diameter The lesion may occur on any part of the body

Clinical Characteristics. The incubation period has not been accurately determined The initial lesion appears as a round firm papule Five to ten days later the clinical syndrome appears suddenly It is characterized by fever, chills sweating, headache, backache and lassitude Typically, these symptoms persist for a week or ten days Regional or generalized *lymphadenopathy and a maculopapular and papulovesicular* rash, usually appearing early in the course of the disease but occasionally not until the fifth or sixth day, are nearly constant features The cutaneous lesions may be scanty or profuse They never become confluent They do not involve the plantar surfaces of the feet nor the palmar surfaces of the hands, and seldom the mucous membranes Temperatures are especially elevated in the afternoons and frequently fluctuate between 98° and 104° F in the course of a day Photophobia is not infrequent

The symptoms subside by lysis, generally from one to two weeks after onset Convalescence may be protracted in severe cases It is possible that a lasting immunity is produced, since no second attacks have been reported, and recovered laboratory animals resist attempted reinfection

Diagnosis The clinical syndrome accompanied by eschar rash and lymphadenopathy together with residence in murine infested premises should direct attention to this disease Up to the present time the geographic distribution eliminates the clinically similar fievre boutonneuse and scrub typhus The constant occurrence of the primary lesion a vesicular rash and vector considerations will aid in differentiation from the other rickettsioses The rash of chickenpox is more superficial and the vesicles are thin and easily broken The lesions of smallpox though initially quite similar to those of rickettsialpox in their deeper firmer character have a different maturation usually becoming pustular with eventual scar formation

Leukopenia is the only significant blood change

Recovery of the infectious agent by inoculation of blood from the patient into white mice is desirable for conclusive laboratory diagnosis of sporadic cases A specific antigen prepared from yolk sacs of infected chicken eggs fixes complement in higher dilutions of convalescent serum than in sera from the related spotted fever group although some cross reaction occurs There is no cross fixation with the other typhus like diseases A rising complement fixation titer against the spotted fever group of antigens will differentiate rickettsialpox from other conditions with which it might be confused Increased *Proteus* OX19 agglutinins have seldom been observed

Treatment Oxytetracycline (Terramycin) Aureomycin and chloramphenicol (Chloromycetin) have all produced beneficial effects against infections with *R akari* As little as 2 5 grams of Terramycin administered early in the disease (an initial dose of 0 5 gram and 0 25 gram thereafter every six hours) induces defervescence in about 24 hours without relapse

Prophylaxis Prevention of infection is dependent upon elimination of mice from residential buildings

11

North Queensland Tick Typhus

C B Philip

A mild rickettsial disease has been reported from both northern and southern areas of Queensland Australia It has many features resembling rickettsialpox This disease designated as North Queensland tick typhus

produces in man a syndrome resembling fièvre boutonneuse The etiologic agent *Rickettsia australis* is capable of intranuclear growth a characteristic of the agents of the spotted fever group Although North Queensland tick typhus is antigenically related to this group it is differentiated by specific complement fixation

Tick transmission of this disease has been assumed on circumstantial evidence The first described infections occurred in troops undergoing training in restricted tick infested areas in North Queensland A history of tick bite was obtained from a majority of the patients some of whom developed eschars at the site of tick bite *Ixodes holocyclus* (Neumann) is suspected of being the most probable vector of the disease Specific complement fixing antibodies have been found in four species of small marsupials (two bandicoots kangaroo rat and brushtail opossum) and in one rat all taken in endemic environs where humans had contracted the disease

The diagnosis of this disease is aided by the presence of an eschar associated with regional lymphadenopathy rash and a typhus like clinical course The Weil Felix reaction is positive for *Proteus* OX19 and OX2 The complement fixation test has not been thoroughly studied in human cases of North Queensland tick typhus However in the guinea pig and rabbit the disease can be differentiated from other rickettsial diseases by specific complement fixation From rickettsialpox this differs not only in epidemiology and serology but also fails to cause frank infection in mice

12

Scrub Typhus

C B Philip

Synonyms Tsutsugamushi disease Japanese river or flood fever
tropical typhus
transmitted by
marked by an
eschar accompanied by regional lymphadenitis

Distribution Scrub typhus has a wide distribution in eastern and southern Asia and the islands of the southwest Pacific It extends from Korea and Japan where several new endemic foci have been found south through Formosa the Philippines Celebes Indonesia New Guinea the northeast coast of Australia and the adjacent island groups as far east

as Espiritu Santo It is likewise endemic in South Vietnam Malaya Thailand Burma India, China Ceylon and islands in the Indian Ocean and the Bay

Yangtse

Etiolo

rickettsiae the electron microscope reveals an outer envelope and an inner matrix with dense granules in the organism (Fig II 16)

Epidemiology. The disease is most prevalent in midsummer in Japan and Korea and in winter in the Izu Islands where it is known as Shichito disease There is no seasonal prevalence in the subtropics and tropics Scrub typhus is a "place" disease Its local distribution depends

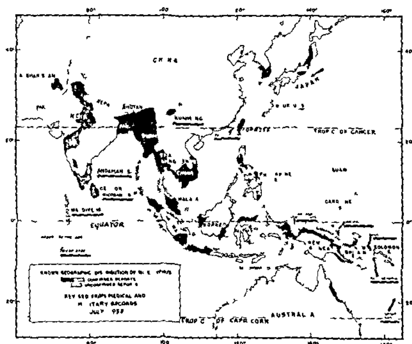


Figure II 15 Geographic distribution of scrub (mite) typhus (Courtesy of C B Philip Rocky Mountain Laboratory)

upon the distribution of the vector mites and infected areas are often extraordinarily discrete and circumscribed Commonly these are grassy or covered with scrub underbrush often associated with flooded river banks although infected mites have been collected even in primary jungle

Two species of mites belonging to the subfamily Trombiculinae have been chiefly incriminated as vectors *Trombicula akamushi* and *Trombicula deliensis* but other trombiculids indigenous to several foci have been found with natural infection and probably function at least in natural maintenance for example *T scutellaris* in the winter focus on the



Figure II 16 Electron photomicrograph of *Rickettsia tsutsugamushi* prepared from yolk sac suspension 23 000 × (Courtesy Department of Virus and Rickettsial diseases Walter Reed Army Institute of Research)

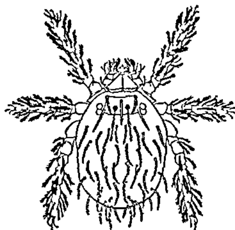


Figure II 17 *Tromb cula akamushi* larva (greatly enlarged) vector of scrub typhus (Nagayo et al Am. J Hyg)

Islands south of Tokyo They probably cause occasional human cases since some of them have been taken off man (Fig II 17)

The infecting agent is acquired and transmitted by the mite only in the larval stage The rickettsiae then survive in the mite through its nonparasitic nymphal and adult stages and are passed through the eggs to the next generation of larvae which are infective and transmit the organisms to new hosts

Field mice rats voles shrews and other small animals which are hosts to the larval mite are probably involved in the natural disease cycle

Pathology. The most characteristic pathologic feature of scrub typhus is the primary ulcer or eschar resulting from the attachment of the infecting mite The regional lymph nodes are markedly enlarged *some of them at times showing central necrosis* and generalized lymphadenopathy is common The body cavities contain moderate amounts of serofibrinous fluid The lungs usually show hemorrhagic pneumonia with secondary lobular pneumonia The liver and spleen are enlarged and there is congestion of the parenchymatous organs

Histologic examination reveals that the vascular system is primarily affected, as in other rickettsial diseases There is widespread focal vasculitis and perivasculitis with accumulations of monocytes, plasma cells and lymphocytes The most striking damage is found in the heart, lung, brain and kidney (Figs II 18, II 19) Focal and diffuse myocarditis is characteristic, interstitial and lobular pneumonia is usual in fatal cases Meningitis and encephalitis may occur with degeneration, and there may [illegible] The kidneys

[illegible] har may be

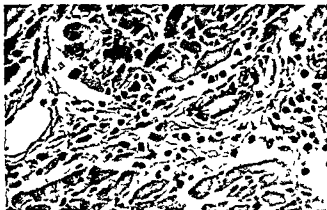


Figure II 18 Scrub typhus monocytic infiltration of heart muscle

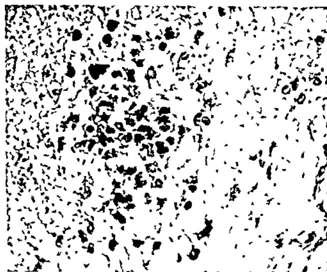


Figure II 19 Scrub typhus nodule in brain showing edema, degeneration and monocytic infiltration.



Figure II 20 Eschar or primary lesion of scrub typhus (Courtesy U S A. Typhus Commission)

found in over 60 per cent of cases It may be located on any part of the body particularly on the clothed surfaces and careful and complete examination of all skin areas may be necessary to find it It begins as a painless papule which slowly enlarges to become crusted Occasionally there may be more than one eschar They range in size from 0 3 to 2 0 cm in diameter (Fig II 20)

Since attachment of the larval mite does not usually produce irritation or itching and since no local symptoms accompany the developing primary lesion the individual frequently is unaware both of exposure to infection and of the existence of the eschar

After an incubation period of from seven to 18 days the disease begins acutely with severe headache fever chilliness and malaise During the first week the fever rises progressively reaching 104° to 105° F while the pulse remains relatively slow seldom exceeding 100 The regional lymph nodes draining the area of the primary lesion are enlarged and tender there is frequently less marked generalized lymphadenopathy and the spleen may be palpable Between the fifth and the tenth day the characteristic red macular rash appears on the trunk and may extend to the arms and legs It usually persists for several days (Fig II 21)

Signs of respiratory involvement appear early with a cough that in more than half the cases is accompanied by physical signs indicative of pneumonitis

During the second week the temperature remains elevated the pulse rate ranges at a higher level and headache apathy conjunctival congestion and varying degrees of deafness are common In severe cases there may be evidence of involvement of the central nervous system with the development of delirium stupor and muscle twitching The systolic blood pressure is commonly below 100 mm Hg

In nonfatal cases the temperature falls by lysis at the end of the second or the beginning of the third week The pulse and blood pressure return to normal and the abnormal physical findings disappear Convalescence is generally prolonged Sequelae in the form of psychiatric difficulties or persisting deafness are not unusual

The mortality has ranged as high as 60 per cent in certain outbreaks However among United States forces during World War II it varied from 0 to 25 per cent in different areas

Experimental infections in human volunteers indicate that recovery is followed by lasting immunity against a homologous strain of *R tsutsugamushi* but that there is little or no immunity to heterologous strains after one or two years

Diagnosis Differential diagnosis may be difficult in some of the regions where scrub typhus is endemic The clinical picture may suggest other rickettsial infections dengue infectious hepatitis typhoid and malaria often malaria is a concomitant infection or a latent malaria may be activated during the acute clinical phase of scrub typhus However the association of a primary lesion or eschar with regional lymphadenitis headache prostration disproportionately low pulse rate fever and leukopenia is highly suggestive Definitive diagnosis must be based on laboratory tests

Previously the Weil Felix reaction had been considered specific giving a positive reaction to *Proteus* OXK but negative ones to OX19 and OX2 However the reaction may be negative in well established cases or on

tients serum by the end of the second week but none develops against

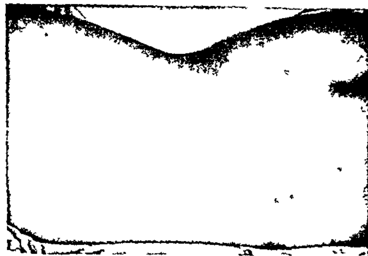


Figure 11.21 Rash of scrub typhus. (Courtesy U.S.A. Typhus Commission)

the OX19 strain Maximum titer is reached by the end of the third week after which they decline rapidly often disappearing by the fifth or the sixth week To have diagnostic significance the Weil Felix reaction must show a rising titer in serial serum specimens (p 65)

Satisfactory antigen for complement fixation is not generally available Unequivocal diagnosis of scrub typhus therefore is based upon recovery of the rickettsiae from the patients blood or tissues or from laboratory animals (see Table II 3 pp 66–67)

within 14 days The peritoneal exudate in these animals contains *R tsu tsugamushi*

Treatment Chloramphenicol (Chloromycetin) tetracycline (Achromycin) chlortetracycline (Aureomycin) and oxytetracycline (Terramycin) are rapidly acting and highly effective therapeutic agents The average time interval between initiation of therapy and completion of defervescence varies between 25 and 37 hours However rickettsemia is demonstrable for 30 to 48 hours after the start of treatment Furthermore when treatment of infected human volunteers is initiated within the first three days of the disease relapses or recrudescences occur in about 50 per cent of patients These respond promptly to further treatment and they may be prevented by a supplementary dose given on the eighth or ninth day after onset The rickettsiostatic effect of the antibiotics apparently persists for a week after the last dose

Administration of Chloromycetin is not associated with toxic or disagreeable side effects and it is the drug of choice Drugs of the tetracycline group may cause gastric irritation nausea and vomiting

DOSAGE CHLOROMYCETIN AND AUREOMYCIN An initial dose of 3 0 grams should be given by mouth followed by an additional 3 0 grams in divided doses during the subsequent 12 to 24 hours

DOSAGE TERRAMYCIN AND ACHROMYCIN 1 5 grams by mouth every six hours until a total of 6 0 grams has been given

The general treatment of scrub typhus is directed toward maintenance of fluid balance and protection of the myocardium

Prophylaxis No effective vaccine is available It has been shown however that exposed personnel can be immunized by antibiotic therapy as above of induced infection where field operations are critical

When it is necessary for an individual to enter mite infested areas in a region where scrub typhus is endemic a high degree of protection may be obtained by rigorous application of three procedures Camp sites should be burned the surface vegetation removed by bulldozer and the area sprayed with dilutions of lindane or dieldrin emulsions All clothing should be impregnated with a 5 per cent dimethyl phthalate emulsion which gives excellent protection against the larval mites until the clothes are washed (see Table XI 10 p 776) Exposed skin areas should be treated every two to three hours with an insect repellent such as dimethyl phthalate (see Table XI 10 p 778)

Although effective chemoprophylaxis has been obtained using Chloro

mycetin in doses of 3 0 to 4 0 grams every four to seven days and continued over a period of four to six weeks after the last potential exposure it is not free from risk and should be used with caution if at all Such long continued administration may contribute to severe secondary infection by *Candida albicans* and to the development of serious blood dyscrasia particularly agranulocytosis

13

Trench Fever

C B Philip

Synonyms. Wolhynia fever Meuse fever quintan or five day fever

Definition Trench fever is a specific relapsing infectious disease transmitted from man to man by the body louse *Pediculus humanus humanus* and caused by *Rickettsia quintana* Blood and urine of convalescents are infectious over a long period

Distribution. The disease has occurred in epidemic form in many parts of Europe in Mesopotamia and Egypt during World War I and in troops on the German Russian frontier in World War II Mooser has recently reported recovery of infection from body lice in Mexico

Etiology *Rickettsia quintana* (= *R pediculi* (?) *R weigli R wolhynica*) appears to be the causative agent as suggested from evidence obtained by infection of human volunteers and transmission by clean laboratory bred lice However inability to grow this agent in laboratory animals in tissue culture and in chick embryos plus the following behavior sets this organism apart from the usual pathogenic rickettsiae *R rocha limae* another organism described from the body louse is probably different because it is highly lethal to the louse but still not pathogenic to man

Rickettsia quintana grows extracellularly in the lumen of the gut of lice fed on a patient or injected intrarectally with the patients blood or in infected louse feces The agent is nonpathogenic for the louse which once infected remains so for life but does not pass the agent transovarially *Rickettsia quintana* is fairly resistant to the usual environmental factors and dried louse feces may remain infectious for several weeks or longer

Epidemiology Epidemics of trench fever have occurred among troops during World Wars I and II and in laboratory personnel on whom lice were being fed in the process of making typhus vaccine by the Weigl

method No other outbreaks among the civilian population have been described although evidence indicates that endemic foci of this disease may exist in certain regions such as Volhynia in Poland the Ukraine and Bessarabia

Transmission of trench fever from man to man takes place through the agency of the infected body louse probably by contamination of the abraded skin with the infective louse feces Man is probably the reservoir of this disease since *R quintana* has been recovered from the blood of convalescents up to eight years after acute illness Although in nearly all convalescents the organism is present in the blood during the illness and for a few weeks afterward its subsequent presence in this tissue may be transitory may last for several months or even years or may be periodic in which case the agent appears for a few weeks at a time at various intervals one or more times a year It also appears that this rickettsia may remain latent in some convalescents for long periods during which the agent cannot be recovered from the blood Latent infections manifested by either frank illness or merely an active blood carrier state have been reported to occur following some unrelated stimuli such as other infections or injections of typhus or antityphoid vaccines

Pathology Biopsy of the exanthematic lesion of trench fever reveals a perivascular infiltration principally of lymphocytes but the vascular intima is normal and there is no thrombotic process The causative organism apparently does not invade cells having been demonstrated only in the circulating blood There are no autopsy reports on trench fever

Clinical Characteristics The symptoms of trench fever are extremely variable making a clinical diagnosis of many cases difficult or impossible Headache malaise and body pains may appear as prodromes toward the close of the ten to 30 day incubation period The actual onset is nevertheless sudden Headache vertigo pain in the back and legs especially in the shins postorbital pain on movement of the eyes often nystagmus on lateral gaze and injection of the eyes accompany a rapid rise of temperature to 103° or 104° F The primary fever continues for several days to a week less often for several weeks The leukocyte count is variable some cases presenting a leukocytosis in others the count is normal or a leukopenia may be present Albuminuria is usual and polyuria common

reg
cute
or in

a relapse The rash consists of small erythematous macules—occasionally papules—that blanch on pressure They are relatively few in number and often disappear within 24 hours Their distribution is characteristic including particularly the chest back and abdomen

Convalescence is frequently prolonged and complicated by a variety of symptoms among which those of functional derangements of the cir

culatory system and neurasthenia are the most common The mortality is negligible

Immunity appears to be variable in duration but its actual development is a controversial question in view of the relapsing character of the disease the periodic nature of the blood carrier state in some individuals and the evidence for the existence of latent infections with *R quintana*

Diagnosis The differential diagnosis of trench fever may include influenza dengue, the dengue like fevers malaria and brucellosis Laboratory tests present the best diagnostic aid and consist of isolation of the agent in lice and of specific serologic tests

Isolation of *R quintana* from the patient in clean laboratory bred lice has provided the most practical means of diagnosis This may be ac- [illegible] ing lice [illegible] Within [illegible] jection organisms appear in the louse excreta Histologic examination of the intestinal lining of the louse is necessary to ascertain that the organisms develop extracellularly Repeated feedings are usually required to infect more than a small percentage of lice Demonstration of *R quintana* in the blood of a suspected patient does not always constitute a definite diagnosis of trench fever since this organism is known to persist for long periods in the blood of convalescents A negative history of past illness with this disease or of residence in louse infested environment aids in the diagnosis

Complement fixation and agglutination employing washed suspensions of *R quintana* prepared from dried infected louse excreta are of reported value as specific diagnostic aids The Weil Felix reaction is negative Attempts to isolate the agent in the usual laboratory animals or to cultivate it in fertile hens eggs have so far been unsuccessful

Prophylaxis The prophylaxis of trench fever depends upon effective measures for louse control (see p 774) The infectious agent is present in the patient s urine during the acute stages of the disease suitable precautions in the disposal of excreta must therefore be emphasized Individuals who have recovered from this disease should not be used as blood donors because of the long persistence of this agent

14

Q Fever

Herbert G Stoener

Synonyms Nine mile fever (United States) Balkan grippe (Greece)

Definition An acute rickettsial disease characterized by remittent fever pneumonitis and the absence of rash

Distribution Practically worldwide except Ireland and the Scandinavian countries

Etiology *Coxiella burnetii* (= *R burnetii R diaporica*) possesses the general characteristics of the rickettsiae as regards association with arthropods cultural characteristics morphology and staining reactions but possesses some distinguishing features This agent passes Berkefeld N filters or collodion membranes with an average pore diameter of 400 mμ is more resistant to certain physical and chemical agents persists for months to years in tick feces has distinct immunologic properties and does not produce agglutinins for *Proteus* X strains Such characteristics of the etiologic agent together with the lack of the usual typhus like rash and Weil Felix serologic findings plus failure of arthropods to play an important role in human infection have resulted in the differentiation of *C burnetii* on a generic level Various strains of *C burnetii* have exhibited only minor differences The agent does not invade the nuclei of host cells

Epidemiology Man probably contracts Q fever by inhaling dust particles contaminated with rickettsiae originating from livestock The agent has been isolated from air samples taken in environments of infected sheep cattle and goats Exposure to infected livestock or their products residence near contaminated premises and household use of *raw milk are factors predisposing to infection* On rare occasions secondary cases have occurred among persons having contact with patients In North America Q fever chiefly affects men of working age The seasonal distribution is uniform in areas where cattle are the major source of infection but a seasonal peak of cases during the post lambing season is characteristic in major sheep raising areas

Although *C burnetii* has been isolated from the milk of cattle sheep and goats the placentas of these hosts are principally responsible for gross environmental contamination Experimental studies indicate that the agent is disseminated among livestock by the air borne route In en

demic areas *C burnetii* infects other hosts (geese pigeons dogs don

livestock remains obscure

Pathology The predominant histopathologic findings in three fatal cases recorded in the literature were associated with bronchopneumonia In red areas of consolidation vessels were intensely congested and alveoli were filled with fibrin containing polymorphonuclear and large mononuclear cells whereas in grey consolidated areas the exudate consisted chiefly of large mononuclear cells lymphocytes plasma cells and few polymorphonuclear cells Lesions observed irregularly include focal testicular infiltration with macrophages focal hypoplasia of the bone marrow and cerebral and pontine softening with thrombi perivascular hemorrhages and an increase in neuroglial cells Rickettsiae were observed in neuroglial cells and in macrophages in the lungs spleen and testis

Clinical Characteristics After an incubation period of about 18 days (range from 12 to 30 days) symptoms appear suddenly The clinical syndrome which varies considerably in severity and duration is characterized by remittent fever chills diaphoresis headache muscle pains malaise and anorexia About one half of the patients develop pneumonitis demonstrable only by x ray and attended by cough scanty expectoration and chest pain Although sequelae (phlebothrombosis and pleural effusions) occur infrequently and the mortality is less than 1 per cent, relapses and protracted convalescences are not uncommon

Roentgenographic findings resemble those seen in cases of primary atypical pneumonia They are first revealed on the third or fourth day and usually persist beyond termination of the febrile period Evidence of pulmonary involvement may occur with mild or inapparent illnesses

Diagnosis. Because Q fever may resemble other acute febrile illnesses a diagnosis should be established by recovery of the organism from the patient or by demonstrating at least a fourfold rise in antibody titer during convalescence When not inhibited by antibiotic therapy antibodies usually appear during the second to third week of illness and may persist for years Cold hemag

including the Weil Felix reaction

Antibodies can be detected by

fixation tests *C burnetii* in animal tissue and early egg passage ("phase 1") is reactive in agglutination tests but it will not fix complement in the presence of specific antibody After a number of egg passages the organism converts to "phase 2" and becomes fully reactive Therefore strains for complement fixing antigens should grow profusely in fertile chicken eggs and should have had at least ten serial egg passages

C burnetii is readily isolated by inoculating hamsters or guinea pigs with blood taken from the patient during the febrile period These ani

mals should be bled 42 days later and their sera tested for specific complement fixing antibodies or test animals can be challenged with a known strain of *C burnetii* In guinea pigs that develop fever and splenomegaly rickettsiae are readily seen in smears of the spleen and the exudate covering this organ A characteristic nonfluctuant indurated skin lesion in which rickettsiae can be demonstrated develops in subcutaneously inoculated animals

Treatment Chloramphenicol and the tetracycline antibiotics usually cause a prompt remission of fever and a subjective improvement of the patient s condition within 72 hours However these antibiotics are not invariably effective since some patients do not respond even when given more than adequate doses The sulfonamides streptomycin and penicillin are ineffective Symptomatic and supportive treatment is indicated particularly in patients severely affected

Prophylaxis Wholly effective means for control of endemic Q fever are not at hand Efforts for their development must be directed against the major animal sources of human infection i e dairy cows sheep and goats but such efforts must await basic epizootiologic studies Vaccination reduces the lacteal shedder rate in infected herds of dairy cattle Vaccination of personnel intensely exposed to infection (e g laboratory personnel) is of proved protective value and is recommended Milk should be pasteurized Careful sterilization of the sputum and excreta of patients is desirable Possible infection from domestic animal pelts which may contain infective tick feces should be considered and mechanical transportation of infective material by flies has been demonstrated in the laboratory

III

Spirochetal Diseases

15

The Relapsing Fevers

Gordon E Davis

Synonyms Tifo recurrente fiebre recurrente febris recurrens fièvre recurrente rückfall fieber rückfall typhus garrapata disease kimputu spirillum fever famine fever tick fever

Definition The relapsing fevers are acute infectious diseases characterized by alternating febrile and afebrile periods caused by spirochetes transmitted through the agency of the louse *Pediculus humanus humanus* and by ticks of the genus *Ornithodoros*

Distribution Louse borne relapsing fever has been reported from all continents It has disappeared from the United States but frequently occurs in parts of South America Europe Africa and Asia Isolated cases in Cuba Brazil and Australia occurring in recently arrived immigrants are said to be louse borne

The tick borne relapsing fevers are widely distributed throughout the Eastern and Western Hemispheres In the Americas endemic centers are known in southern British Columbia Canada in 13 of the western states of the U S A in Aguascalientes in the plateau regions of Mexico in Guatemala and Panama in Central America and in South America chiefly in Colombia Ecuador and Venezuela An endemic focus has also been reported from northern Argentina (Fig III 1)

In Africa with the exception of the Sahara and the rain forest belt the tick borne disease is present from the Mediterranean to Cape Colony and from the Atlantic Ocean to the Red Sea In Europe it is reported

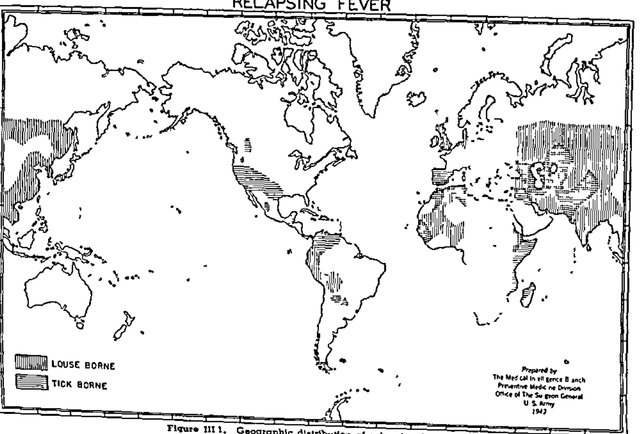


Figure III 1. Geographic distribution of relapsing fever

from Spain, Portugal and the Caucasus In Asia it occurs in Cyprus, Israel, Syria, Turkey, Iraq Iran, in the southern U S S R as far east as the western border of China, in Afghanistan and in Kashmir and Jammu, India

Although indigenous relapsing fever has not been reported from Australia, a strain of *Borrelia* has been recovered from the native rat, *Rattus villosissimus*, in northwest Queensland It is infective for white mice and laboratory rats, but is not known to be pathogenic for man It is suspected that *O gurneyi*, which is present in the north of Australia, may be the vector

Etiology. Relapsing fever spirochetes are loosely wound, flexible coils with tapering ends The number of turns in the coil may vary widely in different strains or in the same strain under varied conditions Multiplication is by transverse fission These spirochetes stain readily with ordinary bacterial stains and especially with the Romanowsky blood stains Attempts to maintain cultures by bacteriologic methods have not met with success Strains are conserved only by frequent animal passage, in the developing chick embryo, or in the specific tick host, where they survive for years even in unfed ticks (Fig III.2)

Although it is generally agreed that the relapsing fever spirochetes constitute a single genus there is little agreement as to the acceptance of any one of the generic names variously designated as *Protomycetum, Spirochaeta Spirillum, Spironema, Treponema* and *Borrelia* The term *Borrelia* is rapidly gaining acceptance *Spirochaeta* has been replaced by

that are similar morphologically afford no basis for classification Staining reactions cross immunity tests serologic reactions and pathogenicity

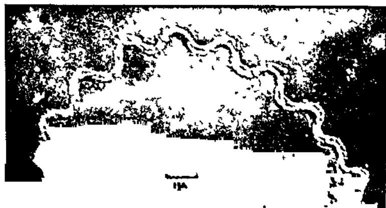


Figure III.2. Electron micrograph of *Borrelia recurrentis* from blood of an infected mouse (Courtesy of Smith & Conant Zinsser's *Bacteriology* 11th ed New York Appleton Century-Crofts, 1957)

Ornithodoros erraticus both large and small forms has a general distribution in northern Africa and spirochetes have been repeatedly recovered from ticks collected over a wide area The tick vectors in Tunisia and northern Libya have not been definitely determined However *O normandi* which feeds on man and from which spirochetes have been recovered is reported to be numerous in rodent burrows near Kef in Tunisia where *O erraticus* is at times found in the same burrows *Ornithodoros tholozani* has been reported from the western Egyptian Desert which extends this species as a potential vector over a considerable area

In the areas east of the Mediterranean *O tholozani is the recognized* vector in Israel Syria Turkey Iraq and Iran It has also been reported responsible for an outbreak of relapsing fever in Cyprus *Ornithodoros tartakovskyi* has recently been found in Iran and spirochetes have been recovered from it

In the U S S R *O tholozani* and *O tartakovskyi* are the reported vectors although little is known concerning the latter species in relation to the disease in man *Ornithodoros tholozani* extends to the western border of China and into Afghanistan In northern India especially in Kashmir and Jammu the tick borne disease is endemic Here *O crossi* (*O tholozani* ?) is the proved vector

In Europe *O erraticus* is the only known vector in Spain and Portugal and *O verrucosus* in the North Caucasus The tick borne disease has been reported from Yugoslavia and Greece but these reports cannot be confirmed

The importance of the several species of *Ornithodoros* as vectors varies directly with their frequency of contact with man *Ornithodoros hermsi* is found in wooded areas at relatively high elevations in the western United States and is brought into houses by tree squirrels (*Tamiasciurus*) and chipmunks (*Eutamias*) from their nests in decaying logs and trees where these ticks have been found in large numbers Once established in dwellings the tick constitutes a permanent reservoir of infection Other house dwelling ticks notably *O moubata* in tropical Africa and *O rudis* in northern South America are in close contact with their human hosts and under such conditions the tick borne disease may approach epidemic proportions in a changing population *Ornithodoros parkeri* found chiefly in the burrows of ground squirrels and prairie dogs (*Cynomys* species) comes in contact with its human host less often and although spirochetes *causing typical reactions in laboratory animals have* been recovered from ticks of this species collected over a wide area in the western United States human cases attributable to *O parkeri* are rare *Ornithodoros turicata* and *O tholozani* when infesting caves or burrows or recesses under overhanging ledges may cause numerous infections among groups of people visiting such areas or using them as a refuge in inclement weather or under the exigencies of war

Pathology The most striking and constant pathologic changes are encountered in the spleen and liver less often lesions are present in the kidney myocardium and central nervous system Jaundice is common in fatal cases and there may be numerous small hemorrhages in the skin

stomach, intestine and kidneys The spleen is usually enlarged and soft and often presents multiple areas of infarction Characteristic miliary lesions are commonly visible in the gross specimen (Figs III 4, III.5) These consist of a zone of congestion and cellular infiltration in which spirochetes are particularly numerous surrounding the malpighian bodies The liver may be enlarged and may present parenchymatous degeneration Spirochetes are commonly demonstrable within the reticuloendothelial cells Areas of degeneration may likewise be found in the kidney



Figure III.4 Miliary lesion in spleen with central necrosis and mononuclear exudate Spirochetes in surrounding zone of infiltration

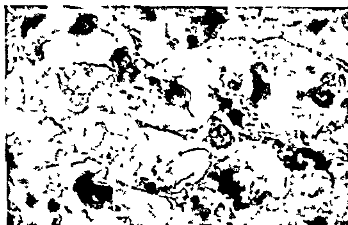


Figure III.5. Spirochetes in lesion of spleen.

and the myocardium Rarely a hemorrhagic meningitis is present and spirochetes may be demonstrable in the parenchyma of the brain

The majority of deaths are due to complications particularly pneumonia

Clinical Characteristics Relapsing fever is characterized clinically by recurring periods of fever and toxemia each of a few days duration separated by afebrile intervals of about a week or ten days Two to ten or more relapses may occur in untreated or improperly treated cases

There is no clinical distinction between the louse borne and tick borne forms of the disease although in general the louse borne variety is said to have a lesser tendency to multiple relapses The mortality usually from 2 to 5 per cent has reached nearly 75 per cent in a serious West African epidemic outbreak

There seem to be rather characteristic variations in the severity of the disease in different areas these variations have led to the consideration of the relapsing fevers in terms of specific geographic regions However there are great variations in severity and clinical phenomena in different cases even within a given area

Thus certain special types have been described such as African tick fever and North African Persian Indian European and American relapsing fever In North Africa the disease is said to be of relatively short duration but frequently complicated by involvement of the central nervous system Facial and ocular palsies are said to be common in this form Jaundice and a somewhat high mortality rate are rather frequent in the Indian form The Persian type of the disease is characteristically mild and the relapses not numerous Relapsing fever in Europe and the Americas is commonly a moderately severe disease however the relapses seldom exceed two or three in number

The incubation period varies from three to ten days The onset is usually sudden associated with vertigo headache myalgia and fever which rises rapidly to 104° to 105° F or even higher The temperature remains elevated with slight daily remissions throughout the primary febrile period Vomiting is common A slight icteric tint of the sclerae is usual In severe cases there may be marked jaundice by the time of the crisis A diffuse bronchitis is frequently present especially in the first febrile episode Transitory erythematous or petechial eruptions are quite common during the initial fever characteristically they are most marked about the neck and shoulder girdle extending later to the chest and abdomen Herpes and epistaxis are also not unusual The spleen is often somewhat enlarged and tender A polymorphonuclear leukocytosis is present from the onset and in patients experiencing high fever and bronchitis may be marked The urine commonly contains albumin and casts and in severe cases hematuria may occur Spirochetes are usually demonstrable in the blood during the febrile periods but not in the apyrexial intervals

After four or five days of severe illness the temperature falls by crisis accompanied by profuse sweating and not infrequently by prostration and signs of cardiac weakness The afebrile period lasts three to ten days, during which time there is usually marked clinical improvement

The relapse sets in acutely and the subjective and objective phenomena are quite similar to those of the initial attack In the relapses conjunctivitis and iritis are often seen and there may be transitory or permanent cranial nerve palsies Deafness likewise is not uncommon and may persist Uterine hemorrhage is not unusual and the pregnant woman frequently aborts Again after a few days of illness the attack terminates by crisis

There are usually four to five such recurrences although occasionally there may be as many as ten or more Late in the course of the disease peripheral neuritis may be persistent and troublesome

Diagnosis In the differential diagnosis relapsing fever may have to be distinguished particularly from malaria dengue and typhus When jaundice is present it may be confused with yellow fever and leptospirosis

The clinical picture and leukocytosis may be suggestive Definitive diagnosis however depends upon detection of the spirochetes These are demonstrable in the blood only during the pyrexial period In some instances they may be seen easily in Giemsa stained blood films In others

l into

found

may

be a continuous spirochetemia for many days and spirochetes may be recovered from the brain of some experimental animals several months after the initial infection

The disease produced in monkeys and guinea pigs resembles the human infection Although guinea pigs are resistant to infection with some strains other strains produce typical febrile relapses with a disappearance of spirochetes from the peripheral blood during the afebrile periods and reappearance at the time of the rise in temperature Hemoperitoneum has been reported as a constant reaction with some tick strains from north Africa Hamsters have been used extensively in the experimental studies

In instances of the louse borne disease spirochetes may be demonstrated by removing lice from the patient grinding them up and inoculating the suspension into mice The demonstration of spirochetes in ticks from the patient however affords only presumptive evidence since some ticks carry spirochetes which they cannot transmit

The Wassermann reaction is positive at times in the acute stage of the disease

Treatment The susceptibility of the spirochetes of relapsing fever to certain drugs and antibiotics varies widely The former concept that arsenicals particularly neoarsphenamine are specific therapeutic agents in a high proportion of cases has been seriously questioned especially during World War II

Two arsenical drugs may prove useful They should be administered intravenously during a rise in temperature as follows

Neoarsphenamine 0 3 to 0 9 gram for adults and 0 005 to 0 01 gram per kilogram of body weight for children for two successive days Adminis

tration of the drug is frequently followed by vomiting elevation of temperature and aggravation of other symptoms

Mepharsen 0 04 to 0 06 gram should be given intravenously on three successive days

Therapy should be instituted as early as possible but should be limited to the early hours of one of the paroxysms Late in the pyrexial period there may be serious reactions to the drug and in the apyrexial intervals it is ineffective

In the louse borne type of relapsing fever penicillin has proved very effective when administered in a dosage of 25 000 units every three hours until 1 000 000 units have been given

A considerable number of cases of the tick borne disease from widely separated areas have been reported as successfully treated with antibiotics especially Aureomycin and streptomycin Others have been treated with combinations of Aureomycin and Terramycin In one series of 68 patients infected with *B hispanica* 0 25 gram of Aureomycin was administered at six hour intervals for a total dose of 3 0 grams In another series of *B persica* infections 0 5 gram of streptomycin was administered twice daily for two days However in the evaluation of any *treatment it should be remembered that in untreated cases* within a limited geographic area relapses vary from one to as many as 14

Prophylaxis Approved methods of protection against ixodid ticks are not applicable to ticks of the genus *Ornithodoros* Biotopes and feeding *habits of the two groups differ widely For the most part* argasid ticks remain within or in close proximity to their host habitats such as burrows caves hollow logs or stumps or in dwellings Wattle huts cracks and crevices in adobe huts floor matting beds fashioned of bamboo *or the rustic bark shingles of more pretentious summer homes* afford excellent harborage for these ticks

Some species feed readily in all stages on man Feeding is rapid and infection may take place less than one minute after attachment The *larvae are extremely small and go unnoticed until the engorged* tick appears red with blood Some species are night feeders and may not be discovered until intensive search has been made A house once infested may be considered always infested It may be necessary to destroy the *more primitive huts by burning Modern homes should* be proofed to prevent ingress of rodent hosts Some of the newer insect repellents may afford protection under bivouac or semibivouac conditions

Avoidance of lice constitutes full prophylaxis against louse borne re*lapsing fever Since the spirochetes are not found in louse feces* it is necessary to make contact with body fluids of crushed lice to acquire the disease Louse control should be rigidly practiced (see p 774)

16

Yaws and Bejel

Yaws

Synonyms Frambesia pian boubá

Definition Yaws is an acute and chronic relapsing infectious contagious nonvenereal spirochetal disease caused by *Treponema pertenue* It is characterized by three stages an initial ulcer or granulomatous cutaneous lesion the "mother yaw" nondestructive secondary lesions of the skin bones and periosteum and finally destructive deforming lesions of the skin bones and periosteum Onset is rare before the age of 18 months The disease may extend over 40 years or more causing ill health and disability Infection produces a slowly developing relative immunity

Distribution Yaws is restricted to the tropical zones where it is widespread in many areas of the world It is especially prevalent in hot moist lowland countries It is common in the West Indies tropical America throughout equatorial Africa Ceylon Malaya Burma Thailand Laos Cambodia Vietnam Indonesia and in the Philippines Samoa and other Pacific islands It is also present in northern Australia but is relatively uncommon in India and China

Etiology The etiologic agent *T pertenue* is a rigid spiral organism with attenuated extremities which is morphologically indistinguishable from *T pallidum* Infection is accompanied by positive serologic reactions as in syphilis The organism has not been grown in artificial culture media It is present in great numbers in the discharges from open primary and secondary lesions

Epidemiology For many years there has been a sharp difference of opinion as to the identity of yaws and syphilis and the exact relationship between these two diseases is still controversial The conservative view however holds that yaws is due to infection by a different but closely related strain of organism It has frequently been observed that syphilis is rare or unknown among populations in which yaws is prevalent

There are important clinical and epidemiologic differences between the two diseases Yaws is not a venereal disease it is not congenital and it is predominantly a disease of childhood The primary lesion of yaws is almost invariably extragenital and is similar to the lesions of the secondary stage of the disease In most skin areas however the "mother yaw" may closely resemble a chancroid

Yaws is a disease strictly of the tropical zones In the colder climates



Figure III 6 Figure III 7

Figure III 6 *Treponema pertenue* in epidermis

Figure III 7 Papular lesion of yaws showing thickening of epidermis elongation and infiltration of papillae and hyperplasia of interpapillary pegs

within the tropics it occurs in modified form and it does not spread when introduced into the temperate zones The incidence is highest among native populations whose level of personal hygiene is low and Europeans are rarely infected It is more common in men than in women

The spirochetes are unable to penetrate unbroken skin and infection occurs directly through contact of cuts abrasions or other cutaneous lesions with an open yaws lesion on another individual or indirectly through soiling of the broken skin with contaminated material It is commonly communicated by person to person contact and primary yaws in an adult is usually confined to nursing mothers who are infected by *their infants*

Flies especially species of *Hippelates* may be mechanical vectors in some areas In general however, insects are of minor importance in transmission

Yaws tends to be a seasonal disease Cases presenting the lesions of the primary and the secondary stages are much more numerous during the rainy season than at any other time of year

Pathology The most characteristic pathologic feature of yaws is the predominant involvement of the skin The organisms are most abundant in the epidermis

The cutaneous lesions consist of granulomatous papules and macules

sists of plasma cells lymphocytes polymorphonuclear leukocytes eosinophils and some increase of large mononuclear cells and fibroblasts Perivascular cell accumulations in the corium are not as characteristic as in syphilis (Figs III 6 III 7)

This process leading to the formation of a smooth papule may be followed by
ficial erosion
to form a cru
the floor of g
granulation tissue then produces the characteristic fungating more or less ulcerated frambesiform lesion which is covered with a dirty yellow crust of dried exudate The epidermis at the margin of the granuloma is thickened and contains many spirochetes

The later lesions of the disease include ulcerating granulomatous nodules of the skin and subcutaneous tissues and indolent ulcers (Fig III 8) Invasion of skeletal tissues produces osteitis and periostitis leading to bone deformities Less often there may be extensive destructive lesions of the nose and hard palate producing the condition known as gangosa (Fig III 9)

Clinical Characteristics After an incubation period of two to eight weeks the initial lesion appears at the site of implantation of the



Figure III 8



Figure III 9

Figure III.8 Yaws chronic ulcers and periostitis
Figure III.9 Gangosa



Figure III 10



Figure III.11

Figure III 10 The primary lesion or mother yaw

Figure III 11 Yaws frambœsiform lesions in a Filipino

spirochete usually at some pre existing break in the skin This mother yaw" resembles the typical granulomatous secondary lesion except that it is often larger and spontaneous healing is less rapid It is frequently present when the secondary eruption appears When it is superimposed on a pre existing ulcer a more extensive and ulcerating lesion is produced The development of the primary yaw is accompanied by moderate systemic symptoms aching of the limbs and joint pains and often there is irregular fever There may be enlargement of the regional lymph nodes

The secondary or generalized stage of the disease begins a few weeks to four months after the appearance of the initial lesion Secondary lesions usually appear as elevated apparently granulomatous papules scattered over the surface of the body These vary from a few millimeters to 50 mm or more in diameter and tend to be round or oval At first the surface is composed of greatly proliferated epithelium exuding clear serum which contains great numbers of spirochetes Later a crust develops yellow at first but becoming discolored by debris In young children suffering from anemia or malnutrition the lesions may not be elevated *but appear as erosions with bright pink borders and whitish centers* The eruption may involve the palms of the hands or the soles of the feet The plantar lesions are painful and disabling

Successive eruptions often appear before the preceding ones heal The later lesions tend to be most numerous about the lips axillae genitalia and anus Although typical generalized secondary lesions probably do not occur more than two to three years after the primary eruption secondary lesions about the lips or on the soles of the feet may recur after many years (Figs III 10 III 11)

In cooler environments the skin lesions may be restricted to condyloma

like processes limited to the perianal perineal and axillary regions Healing of the secondary lesions leaves only slight scarring and the scars are never permanently atrophic and pigmented

Nondestructive lesions of the bones are frequent in the secondary stage The characteristic changes are focal rarefactions—rarefying osteitis and periostitis These develop rapidly and usually resolve spontaneously in a few weeks or months The rarefaction disappears but the periosteal reaction may lead to thickening of the bone Goundou and saber shin may be the result of this process (Fig III 12)

The tertiary stage of yaws commonly does not appear until after a relatively or completely symptom free interval of several years A negative Kahn test during this quiescent period indicates termination of the infection A positive reaction is an indication of latency

The appearance of tertiary lesions is the only evidence of the beginning of the final stage These destructive changes do not occur in the presence of the secondary eruption Although they may develop within a few years after infection they reach their highest incidence in the third and fourth decades of life In this stage resolution and spontaneous cure may occur or the disease may again become latent with the subsequent appearance of relapsing tertiary lesions



Figure III.12. Saber shin of late yaws (Alan Fisher for the Office of the Coordinator of Inter American Affairs)

The lesions of the skin are characteristically of three types There may be extensive spreading superficial and relatively clean ulceration ultimately healing from the center Cutaneous and subcutaneous nodules develop which break down to form deep indolent ulcers with irregular bases Spirochetes cannot usually be demonstrated Healing proceeds from the margin and from isolated islands in the base producing atrophic



Figure III 13 Yaws hyperkeratosis with fissuring of the soles of feet crab yaws

scars These may be unpigmented in the early stages but later are often deeply pigmented and may cause severe contractures Hyperkeratotic lesions of the soles of the feet and less commonly of the palms of the hands cause extensive thickening of the skin with fissuring and ulceration These "crab yaws are painful and the source of severe disability (Fig III 13) In different parts of the world they constitute from 40 to 90 per cent of all yaws cases They are most common in young adults particularly men and develop especially during the rainy season and after trauma

Destructive bone and periosteal lesions are frequent They resemble the gummata of syphilis and are usually single or few in number They develop slowly and may extend through the subcutaneous tissues and the skin to produce chronic ulceration which responds only slowly to treatment They are accompanied by local swelling tenderness and pain The tibia other long bones and the bones of the hands are most commonly involved Less frequently lesions occur in the tarsal and carpal bones the skull clavicles scapulae and sternum Involvement of the hard palate leads to perforation and the process may progress causing extensive destruction of the structures of the nose to produce gangosa (Fig III 9) Joint lesions are not uncommon and fibromatous tumors in the vicinity of the appendicular joints—juxta articular nodules —are often associated with the late lesions of yaws

Diagnosis The diagnosis of yaws may often be made on clinical grounds as the typical generalized lesions are not easily confused with other diseases Confirmation is made by the demonstration of spirochetes in a dark field examination of exudate from the lesion or by a smear stained by Giemsa s method Spirochetes may likewise be demonstrated by India ink preparations The Wassermann and Kahn reactions of the blood are positive but such tests of the cerebrospinal fluid are usually negative

The lesions of mucocutaneous leishmaniasis may be confused with the nasopharyngeal manifestations of yaws Similarly ulcerating lesions of leprosy and tuberculosis may present differential diagnostic problems the solution of which will depend upon demonstration of the specific etiologic agents

The differential diagnosis between late lesions of yaws and syphilis especially those affecting bony structures may be extremely difficult if not impossible The history and presence of a scar from a healed "mother yaw" are important

Treatment. The response of early infectious yaws to antibiotic therapy is dramatic and total eradication of the disease is now possible The use of arsenical drugs and bismuth is not recommended

Primary and Secondary Yaws Penicillin is the drug of choice in the treatment of infectious yaws One injection of procaine penicillin in 2 per cent aluminum monostearate and oil in doses of not less than 1 200 000 units for adults and proportionately less for children is recommended for treatment of the usual case The response to this therapy is very rapid The infectious lesions become darkfield negative within 48 hours and healing is complete within one week Serologic titers decline rapidly but a substantial group of patients may show a low titer for several months following therapy Serologic tests should be repeated at three month intervals and the treatment repeated if the serologic findings remain positive after six months

Tertiary Yaws The late lesions of yaws are much more resistant and repeated therapy may be required to accomplish healing and render the patient serologically negative In addition to penicillin the broad spectrum antibiotics may be effective

Oxytetracycline and chlortetracycline have been found to be of great value in the treatment of indolent ulcerations gummas and deforming osteoperiostitis These drugs are given orally 2 grams daily for five to ten days in adults and proportionately smaller doses in children Oxytetracycline given intramuscularly 150 mgm once daily may be of value when extensive lesions are resistant to penicillin or the broad spectrum antibiotics may be given orally in such cases

Ulcerations of late yaws should be treated concomitantly with local antiseptic dressings The hypertrophied nasal bones of goundou must be excised surgically Other deformities such as contractures or chronic osteitis may also necessitate surgical relief either plastic operations or amputation although the response of such advanced lesions to chemotherapy alone is sometimes satisfactory if the pathologic process is still in an active stage

Control. The primary objective of yaws control campaigns is to eliminate the infectious primary and secondary lesions from the population It is not to effect radical cure of the disease A single injection of penicillin has proved to be completely effective for such control operations

Prophylaxis. The prevention of yaws consists essentially of avoidance of infected contacts and the adequate protection of open infectious lesions In areas where the disease is endemic mass therapy constitutes



Figure III 13 Yaws hyperkeratosis with fissuring of the soles of feet crab yaws

scars These may be unpigmented in the early stages but later are often deeply pigmented and may cause severe contractures Hyperkeratotic lesions of the soles of the feet and less commonly of the palms of the hands cause extensive thickening of the skin with fissuring and ulceration These "crab yaws" are painful and the source of severe disability (Fig III 13) In different parts of the world they constitute from 40 to 90 per cent of all yaws cases They are most common in young adults particularly men and develop especially during the rainy season and after trauma

Destructive bone and periosteal lesions are frequent They resemble the gumma of syphilis and are usually single or few in number They develop slowly and may extend through the subcutaneous tissues and the skin to produce chronic ulceration which responds only slowly to treatment They are accompanied by local swelling tenderness and pain The tibia other long bones and the bones of the hands are most commonly involved Less frequently lesions occur in the tarsal and carpal bones the skull clavicles scapulae and sternum Involvement of the hard palate leads to perforation and the process may progress causing extensive destruction of the structures of the nose to produce gangosa (Fig III 9) Joint lesions are not uncommon and fibromatous tumors in the vicinity of the appendicular joints—juxta articular nodules—are often associated with the late lesions of yaws

Diagnosis The diagnosis of yaws may often be made on clinical grounds as the typical generalized lesions are not easily confused with other diseases Confirmation is made by the demonstration of spirochetes in a dark field examination of exudate from the lesion or by a smear stained by Giemsa's method Spirochetes may likewise be demonstrated by India ink preparations The Wassermann and Kahn reactions of the blood are positive but such tests of the cerebrospinal fluid are usually negative

The lesions of mucocutaneous leishmaniasis may be confused with the nasopharyngeal manifestations of yaws Similarly ulcerating lesions of leprosy and tuberculosis may present differential diagnostic problems the solution of which will depend upon demonstration of the specific etiologic agents

The differential diagnosis between late lesions of yaws and syphilis especially those affecting bony structures may be extremely difficult if not impossible The history and presence of a scar from a healed mother yaw are important

Treatment *The response of early infectious yaws to antibiotic* therapy is dramatic and total eradication of the disease is now possible The use of arsenical drugs and bismuth is not recommended

Primary and Secondary Yaws Penicillin is the drug of choice in the treatment of infectious yaws One injection of procaine penicillin in 2 per cent aluminum monostearate and oil in doses of not less than 1 200 000 units for adults and proportionately less for children is recommended for treatment of the usual case The response to this therapy is very rapid The infectious lesions become darkfield negative within 48

ic titers decline
a low titer for
be repeated at

three month intervals and the treatment repeated if the serologic findings remain positive after six months

Tertiary Yaws The late lesions of yaws are much more resistant
d to accomplish healing and render
n addition to penicillin the broad

Oxytetracycline and chlortetracycline have been found to be of great value in the treatment of indolent ulcerations gummas and deforming osteoperiostitis These drugs are given orally 2 grams daily for five to ten days in adults and proportionately smaller doses *in children Oxytetra*cycline given intramuscularly 150 mgm once daily may be of value when extensive lesions are resistant to penicillin or the broad spectrum antibiotics may be given orally in such cases

Ulcerations of late yaws should be treated concomitantly with local antiseptic dressings The hypertrophied nasal bones of goundou must be excised surgically Other deformities such as contractures or chronic osteitis may also necessitate surgical relief either plastic operations or amputation although the response of such advanced lesions to chemotherapy alone is sometimes satisfactory if the pathologic process is still in an active stage

Control The primary objective of yaws control campaigns is to eliminate the infectious primary and secondary lesions from the population It is not to effect radical cure of the disease A single injection of penicillin has proved to be completely effective for such control operations

Prophylaxis The prevention of yaws consists essentially of avoidance of infected contacts and the adequate protection of open infectious lesions In areas where the disease is endemic mass therapy constitutes

an important control measure No methods of artificial immunization are available

Bejel

Bejel is a chronic infectious nonvenereal treponematosis occurring in Arabs on the deserts of Syria and Iraq There is much argument whether this disease is a form of syphilis or of yaws since it resembles the former in its frequent exhibition of mucous patches and the latter in its affinity for children The blood Wassermann reaction is positive A condition resembling crab yaws is common and juxta articular nodules have also been noted in many of the cases

17

Pinta

Synonyms Mal del pinto carate azul boussarole tina lota empeines

Definition Pinta is an acute and chronic nonvenereal treponematosis caused by *Treponema carateum* The disease is characterized by a superficial nonulcerative primary lesion a secondary eruption and late depigmentation and hyperkeratosis of the skin Pinta is limited almost exclusively to dark skinned races The hands and wrists are involved most frequently although other common sites are the feet and ankles

Distribution Pinta is a disease primarily of the Western Hemisphere occurring in many parts of the American tropics It is especially prevalent in Mexico and Colombia

Etiology Formerly thought to be a superficial mycosis pinta is now known to be caused by a spirochete morphologically identical with that of syphilis The organism *Treponema carateum* has not been cultivated or successfully inoculated into laboratory animals (Fig III 14)

Epidemiology The method of spread is unknown *Treponema carateum* has been found in the fluid oozing from fissures in hyperkeratotic lesions of the disease so that direct contact is suggested as the means of infection Flies feeding on open sores are suspected of carrying the spirochetes from person to person No evidence of congenital transmission has been reported The highest incidence of the disease is among young and middle aged adults It is most prevalent in hot humid areas

Pathology The epidermis and corium are both involved in a low grade inflammation which results in (a) a disturbance of the melanophores and (b) a thickening of the corium Spirochetes have been dem

onstrated in histologic sections of early skin lesions Visceral lesions have not been proved

Clinical Characteristics. Three stages have been described The first is that of the initial papular lesion, the second is characterized by a spreading eruption of flat erythematous lesions known as pintids (Fig III 15) These two periods occupy about a year In the tertiary stage



Figure III 14 Pinta *Treponema carateum* in epidermis



Figure III.15 Secondary lesion or pintid on right cheek



Figure III 16 Late pinta—areas of complete depigmentation of skin (Courtesy of D Howard Fox)

pigmentary disturbances become manifest often consisting first of variously colored patches and progressing finally to leukoderma (Fig III 16) Not infrequently these are symmetrically distributed Hyperkeratoses appear simultaneously on the palms and soles causing inconvenience if fissuring occurs Pinta rarely causes disabling illness or death

Syphilis apparently does not confer immunity to pinta

Diagnosis Symmetric vitiligo of the hands and possibly the feet in a dark skinned native of tropical America is probably pinta The blood Wassermann reaction is usually positive in the tertiary stage and an eosinophilia is often present

Treatment
treatment of tl
promptly and
regain pigment after antibiotic therapy

Prophylaxis Although the epidemiology of pinta has not been fully studied it is probable that the measures applicable to yaws are efficient in the control and prevention of this disease

18

The Leptospiral Diseases

Robert H Yager and William S Gochenour

The leptospiras causing disease in man are considered to be native to animal hosts reaching man through contamination of food or water by the urine and feces of infected animals These diseases are distributed throughout the world coextensively with the geographic distribution of the normal mammalian hosts

Etiology The genus *Leptospira* is comprised of two major groups of morphologically indistinguishable organisms The saprophytic free living leptospiras can be cultivated on Hindle s feces medium whereas the pathogenic leptospiras require a substrate containing animal serum or tissue extracts

The leptospiras range from 4 to 40 μ in length and are approximatel 0 1 μ in diameter An axial filament f
of the
lon
In move in a serpentine fashion Lepto
spiras readily penetrate mucous membranes and
filter pads
the fresh st
best shown

The pathog
lis They are r temperatures but will survive at −50 C for at least six months The optimum pH ranges are from pH 6 8 to pH 7 6

No valid criteria exist for subdivision of the pathogenic members of the genus into species Classification is based upon serologically de monstrable antigenic differences The leptospiras of significance in North America are shown in Table III 2

Epidemiology Leptospiral characteristic
l and proto-
genus may
The lepto
the tubules of the kidney
urine of these carriers
organisms may
for several wee



Figure III 17 Electron photomicrograph of *Leptosp ra hyos* chromium shadowed showing typical sp ral shape and ax al f lament entwined along the central cell mass (10 600 ×) (Courtesy of Breese Gochenour and Yager in Proc Soc Exper Biol & Med 80 165–188 1952)

The natural reservoirs of infection are rodents small carnivores and certain domestic animals In general each leptospiral serotype has a primary mammalian host within a given geographic area however a *single animal species may be the primary host of several serotypes* and may be simultaneously infected with and shed two or more leptospiral serotypes Development of the carrier state in the several animal species appears in general to be related to their position in the phylogenetic scale Rodents small carnivores and marsupials seem to be almost commensally related to the leptospiras since virtually no apparent disease occurs following infection and a lifelong renal carrier state is established

Domestic animals are less adaptable Clinical disease occurs frequently but the renal carrier state when established is of limited duration Leptospiruria in cattle horses and dogs does not usually persist for more than a few months Swine have been shown to shed leptospiras for at least one year The organisms likewise are present in the milk during the acute systemic phase of the disease in cattle Despite the fact that they will survive in fluid raw milk for a number of hours and in diluted milk for several days no proved case of milk borne leptospirosis of man has been reported

Ticks and horse flies have been shown experimentally to be capable of mechanically transmitting leptospirosis Despite this epidemiologic

Table III 2 North American Leptospiras

SEROGROUP	HOSTS
Icterohemorrhagiae	Norway rat mongoose dog mouse man
Canicola	Dog swine man cattle
Pomona	Cattle swine horse man skunk raccoon wildcat opossum
Bataviae	Norway rat mongoose mouse man
Ballum	Norway rat mouse opossum raccoon gray fox wildcat striped skunk
Autumnalis	Man opossum raccoon
Grippotyphosa	Man raccoon
Australis A	Raccoon opossum
Hyos	Opossum raccoon
Hebdomadis	Man raccoon opossum cattle
Pyrogenes	Man

evidence would indicate that arthropod vectors are not significant in the transmission of infection from animal reservoirs to man

Infections of man result from direct or indirect contact with the contaminated urine of an animal carrier Infection may occur through the mucous membranes or through minute cuts or abrasions of the skin Penetration of intact skin has not been conclusively proved Although the acidity of the stomach is sufficient to destroy ingested leptospiras infection may take place by penetration of the buccal pharyngeal and esophageal mucous membranes

The epidemiologic importance of particular animal carriers depends upon their collective mode of life The population density and the rate of increase are important since the chain of infection can be maintained only when adequate numbers of susceptible animals are constantly available Thus in the serogroup Bataviae infections of man in the rice fields of northern Italy the sudden increase of human cases in early July of each year corresponds with the appearance of large numbers of dwarfed mice and the resulting high degree of contamination of the fields

Leptospirosis is often an occupational disease The serogroup Icterohemorrhagiae infections are commonly found in miners sailors sewer workers and abattoir workers Canicola infections are most frequently seen in animal caretakers particularly the owners and breeders of dogs Grippotyphosa infections occur in farmers agricultural workers pea pickers and flax workers Pomona infections are seen in swineherds creamery and cheese workers swine slaughterers veterinarians and animal husbandrymen

Leptospirosis is primarily a disease of young adult men because of their greater opportunities for contact with infected environments There is no difference in susceptibility between men and women or between different age groups Epidemic outbreaks occur when groups of persons come into contact with a highly contaminated environment

The leptospiroses of man are acute febrile diseases protean in nature and presenting a wide variety of clinical syndromes which differ greatly

in severity They fall naturally into two groups the classic leptospiral jaundice (Weil's disease) and the benign leptospiroses

Leptospiral Jaundice

Synonyms Weil's disease spirochetal jaundice, mud fever

Definition Leptospiral jaundice is a febrile infection characterized in severe cases by fever vomiting jaundice hemorrhage and enlargement and tenderness of the liver The mortality has varied from 4 to 48 per cent in different outbreaks

Distribution It has a worldwide distribution corresponding to that of the different natural reservoir hosts The disease is most prevalent in regions where rodents are numerous particularly in warm moist tropical areas

Etiology The disease may be produced by any member of the pathogenic group of the genus *Leptospira*

Pathology The principal pathologic changes are seen in the kidneys the liver and the skeletal muscles Hemorrhages are common in the skin the mucosa the viscera and the calf muscles

The liver is usually somewhat enlarged and exhibits varying degrees of *parenchymal degeneration* and areas of *focal necrosis* More rarely the lesions resemble those of acute yellow atrophy Leptospiras are easily demonstrated in tissue sections by the Levaditi stain

The kidneys are swollen and show degenerative changes and necrosis of the epithelial cells of the convoluted tubules Between the tubules infiltration by lymphocytes and mononuclear cells occurs and hemorrhage is not uncommon leptospiras may be numerous (Fig III 18)

Clinical Characteristics. The incubation period *is usually six to 12* days and the onset is abrupt with high fever ranging from 102° to 104° F headache chills prostration and myalgia Anorexia nausea and vomiting are not uncommon Frequently there is a relative bradycardia The face is flushed the conjunctivae injected and petechial hemorrhages are frequent At times bronchopneumonia may be present and the

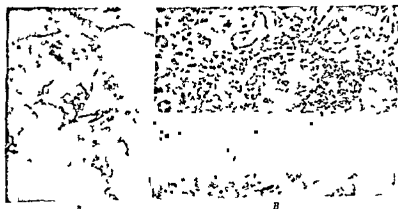


Figure III 18 A Levaditi stain *Leptospira icterohaemorrhagiae* in kidney B Cellular infiltration degeneration of epithelial cells of the convoluted tubules

sputum may contain blood The muscles of the legs especially the calf muscles are tender and there are often signs of meningeal irritation Leptospiras are present in the blood for the first three or four days After two to five days the temperature tends to be lower and the pulse rate elevated A polymorphonuclear leukocytosis of 10 000 to 50 000 is present from the onset accompanied by an increase of immature forms

In the more severe cases jaundice appears usually about the fifth day and may become intense accompanied by enlargement and tenderness of the liver the spleen is only rarely enlarged At the same time evidence of impairment of renal function appears with oliguria of varying severity and nitrogen retention The hemorrhagic tendency may be marked in this phase with petechial or purpuric spots in the skin and mucosae and occasionally gastrointestinal hemorrhage with hematemesis and melena Meningism may be extreme accompanied by increased spinal fluid pressure and pleocytosis composed principally of lymphocytes Herpes is frequent and a varying skin rash (erythematous papular urticarial or purpuric) may be present Leptospiras are present in the urine during this stage and are most numerous from the tenth to about the twentieth day Death occurs in approximately 30 per cent of the jaundiced or severely ill patients most commonly between the ninth and the 16th days

In nonfatal cases improvement usually begins in the second or third week with increased urinary secretion and clearing of the jaundice Convalescence may be prolonged

For **Diagnosis** **Treatment** and **Prophylaxis** see these headings under Benign Leptospirosis (below)

Benign Leptospirosis

Synonyms Fort Bragg fever seven day fever swineherds disease

Clinical Characteristics. Benign leptospirosis is characterized by the absence of jaundice a milder course and favorable outcome The fever is of shorter duration headache and myalgia are less intense and hemorrhagic manifestations are far less common Congestion of the conjunctival vessels remains a very characteristic sign in the early stage of the disease Renal and vascular complications do not occur Meningeal features however are often pronounced and may run a protracted although benign course Occasionally the cutaneous manifestations may be the most characteristic feature of the disease Toxicity disappears rapidly with defervescence

Diagnosis. The severe forms of leptospirosis may be confused on clinical grounds with viral hepatitis poisoning by certain toxic agents or other severe diseases manifesting hepatic renal and vascular derangements [illegible]

In eithe [illegible]

for defi [illegible]

stration of the organisms or by serologic methods (pp 831–833)

Leptospiras are present in the blood and cerebrospinal fluid during the initial febrile phase of the disease They are more easily recovered by direct culture in Fletchers or other suitable media (see p 825) than

by inoculation of laboratory animals Multiple cultures using minimal quantities (about 0 03 ml) of inoculum should be employed and cultures should be incubated at 30° C for at least 28 days before being discarded as negative Direct dark field examination of blood or other fluids rarely reveals the organisms and often yields confusing artefacts

A fourfold rise of antibody titer of paired serum specimens demonstrated by complement fixation or by agglutination lysis may be accepted as diagnostic (p 831) The first specimen should be obtained early in the disease and the second two weeks later Complement fixing antibodies are usually first demonstrable about the 11th day of disease and reach maximum levels in the third week Agglutinating antibodies are first detectable about the 12th day of disease reach maximum levels in the third week and may persist in high titer for many months or years

Leptospiras may be demonstrated by biopsy or at autopsy in liver calf muscle or kidney Silver impregnation techniques are most appropriate for this purpose

Treatment A minimum of five days of antibiotic therapy is recommended Penicillin (3 000 000 units daily) streptomycin (2 0 grams daily) or the tetracyclines (2 0 grams daily) have been shown to be effective if therapy is initiated no later than the second day of illness If antibiotic administration is delayed beyond this time it is of little or no value Supportive and symptomatic treatment is essential

Prophylaxis The great number of leptospiral serotypes which fail to elicit cross immunity makes prophylactic vaccination in man feasible only in cases of specific occupational hazards of infection with single serotypes Preventive measures must at present be directed to control of wild life reservoirs of infection and the prevention and therapy of leptospirosis in domestic animals

19

Rat-Bite Fevers

Robert H Yager and William S Gochenour

The term rat bite fever is employed to designate either of two febrile infections of man characterized by fever of sudden onset myalgia exanthemata leukocytosis and frequent febrile relapses during the course of the disease The microorganisms *Spirillum minus* causing Sodoku and *Streptobacillus moniliformis* which produces Haverhill Fever are har

bored in the nasopharynx of infected rats The mortality in man is approximately 10 per cent

Sodoku

Definition. Sodoku is a relapsing type of spirochetal infection transmitted by the bite of rats infected with *Spirillum minus* It is characterized by a delayed local inflammatory reaction at the site of the wound accompa

fever of sudden

Distribution

be anticipated that cases will be found wherever rats are prevalent and in close association with man Proved cases have been reported from Great Britain Holland Germany Italy East Africa French Equatorial Africa the United States the West Indies South America the Philippine Islands Indonesia Australia and India



Figure III 19 *Spirillum minus in blood film.*

Etiology *Spirillum minus* varies considerably in size usually ranging between 2 and 5 μ in length by about 0 2 μ in diameter Much longer forms may be seen The coils are uniformly spaced about 1 μ

Leptospira and other spirochetes resembling the movements of the vibrios It is doubtful if it has been cultivated in artificial media (Fig III 19)

Spirillum minus is present in the blood of infected rodents during the first two weeks Thereafter it localizes in connective tissue especially about the lips tongue and nose It has not been found in the saliva but is reported to be present in the lachrymal secretions of infected experi

mental animals Transmission by the bite may occur from this source or by escape of the organisms through breaks in the mucous membrane of the rat's tongue or lips

Epidemiology. A number of rodents serve as the normal reservoirs of *S minus*, and the infection rate varies markedly in different areas Thus in Japan infection rates of about 25 per cent and 3 per cent, respectively, have been reported in the rats, *Rattus norvegicus* and *R rattus alexandrinus*, whereas in the vole, *Microtus montebelloi*, the rate is 12 to 54 per cent In Bombay a rate of 11 per cent has been found in the bandicoot, *Nesokia bengalensis* In other parts of the world rates up to 18 per cent have been reported in rats

Pathology. The pathologic process in man has not been studied thoroughly Degenerative changes in the liver and kidneys and hyperemia of the cerebral cortex have been reported The spinal fluid pressure may be increased The organisms are present at the site of the bite and may be recovered by animal inoculation of material aspirated from enlarged lymph nodes, or of blood taken in the early stages of the disease

Inoculated guinea pigs or white rats may show lymphadenitis, enlargement of the spleen, and occasionally spirilli in the blood The liver may be congested and contain scattered organisms Most strains are fatal to guinea pigs within one to two months after inoculation

Clinical Characteristics. After an incubation period which varies usually from five to ten days, rarely extending to five or six weeks, there is sudden onset of fever rising rapidly to 101° or 102° F, accompanied by headache, nausea, marked weakness, tachycardia and often by chills The site of the infecting bite, frequently healed, is inflamed and edematous and may show vesiculation or necrosis with subsequent ulcer formation This is accompanied by superficial lymphangitis and involvement of the regional lymph nodes An eruption of purplish macules or papules is not uncommon, occurring chiefly on the chest and arms Urticaria may be present Joint pains, motor and sensory disturbances and indications of renal irritation may occur During the febrile period there is an eosinophilia and a polymorphonuclear leukocytosis usually ranging from 15,000 to 20,000

The initial fever commonly rises to about 104° F by the second or third day and remains elevated for two or three days more, thereafter falling rapidly to normal Local secondary infections of the wound may complicate the clinical picture

Following the decline in temperature there is usually an apyrexial interval of several days during which the local manifestation at the site of infection and the lymphadenopathy subside Successive febrile paroxysms of decreasing severity are common, the temperature curve resembling that of relapsing fever

Diagnosis. A history of rat bite, together with the clinical phenomena of the initial fever, is suggestive The Wassermann reaction may be positive or negative Dark field examination of the blood or of material from an infected lymph node may reveal *S minus* in early cases Animal inoculation, however, is frequently necessary for recovery of the organisms

formly satisfactory

Haverhill Fever

Synonym Erythema arthriticum epidemicum

Definition Haverhill fever is a febrile disease characterized by an exanthem and more or less severe generalized arthritis It is caused by infection with *Streptobacillus moniliformis* and is transmitted directly or indirectly by rats

Distribution The disease has been reported from the United States the British Isles and Europe

Etiology *Streptobacillus moniliformis* is a gram negative non motile pleomorphic bacillus which grows in irregular chains It is cultivated best in media enriched with 10 to 30 per cent serum or ascitic fluid incubated at 37° C under aerobic conditions Intraperitoneal inoculation of white mice causes a fatal infection terminating in 24 to 48 hours

Epidemiology Man usually acquires the infection from the bite of an infected rat or other rodent One outbreak of milk borne infection has been reported presumably due to contamination of milk by infected rats

Clinical Characteristics A brief incubation period is followed by sudden onset of irregular fever which may persist for weeks or months in untreated cases Early in the disease a reddish maculopapular rash appears on the hands arms and feet which fades on pressure Generalized arthritis of varying severity is common Necrosis and ulceration at the site of inoculation rarely occur

Diagnosis The diagnosis is established by recovery of the organism in culture from blood synovial fluid or wound serum or by demonstration of a specific agglutination titer of 1/80 or above in the patient s serum (p 827)

Treatment. Penicillin (3 000 000 units daily) or tetracycline (2 0 grams daily in divided doses) administered for a period of a week to ten days is reported to be efficacious

Prophylaxis The general prophylaxis consists of effective rodent control Wounds produced by rat bites should be promptly cauterized

IV

Bacterial Diseases

20

The Diarrheal Diseases—Introduction

Revised by Arcey C Sanders

The diarrheal diseases include the simple diarrheas and the dysenteries They are widespread throughout the world and occur wherever local sanitary conditions permit the contamination of food and water with human feces A polluted water supply insanitary feces disposal and the house fly are the most important means of transmission

Clinically the simple diarrheas resemble the dysenteries A variety of etiologic agents may be concerned and local clinical designations without reference either to the nature of the causative organism or to the response of the host are common in many parts of the world Specific diagnosis is made in only a small proportion of cases

Differentiation between the simple diarrheas and the dysenteries depends upon the reaction of the host rather than upon the classification of the infectious agent It is based upon the presence or absence of an inflammatory reaction in the intestinal wall which is indicated by the microscopic characteristics of the stool In the simple diarrheas there is no inflammatory reaction and consequently there is no inflammatory cellular exudate in the stool In the dysenteries on the other hand inflammation is present and this is accompanied by a characteristic exudate in the stool consisting of erythrocytes polymorphonuclear leukocytes and large mononuclear phagocytic cells the macrophages

Table IV.1. The Bacterial Diarrheas and Dysenteries

DISEASE	ORGANISM
Typhoid fever	*Salmonella typhosa*
Paratyphoid fever	*Salmonella paratyphi*, *Salmonella schottmuelleri*, *Salmonella typhimurium*, Other *Salmonella* species
Cholera	*Vibrio comma* (*cholera*)
Bacillary dysentery	*Shigella dysenteriae*, *Shigella flexneri*, *Shigella boydii*, *Shigella sonnei*, Alkalescens-Dispar group
Enteritis	*Salmonella hirschfeldii*, *Salmonella oranienburg*, *Salmonella* [illegible], Other *Salmonella* species, paracolon group
Food poisoning	*Salmonella* species (*Salmonella enteritidis* most common), *Staphylococcus* species (usually the hemolytic, salt-resistant, mannite-fermenting strains), *Streptococcus* species, particularly those strains of Lancefield's groups A, C, D and G, *Clostridium perfringens*

Etiologic Agents The etiologic agents (Table IV 1) include various bacteria, certain protozoa, and certain helminthic parasites. The part played by the various viruses isolated from stools is not clear. Only the bacterial diarrheas and dysenteries will be considered in this section. Typhoid, paratyphoid and cholera infections are included in the classification of the diarrheal diseases because of their high endemicity in certain parts of the world and because they may require consideration in differential diagnosis, especially in partially immunized individuals.

Most of these agents produce a true infection of the intestinal tract with an inflammatory reaction of greater or less severity. The paracolon organisms form a loose and indefinite group, some members of which seem closely related to *Salmonella* and others to *Escherichia*. Although

fection of the host

Differential Diagnostic Procedures Differentiation of simple diarrheas from the dysentery infections is of great importance in clinical management and affects the prognosis, since the therapeutic indications may be quite different. This differential diagnosis entails four essentials:

1 Microscopic examination of the fresh stool for the presence of exudate.

2 Character of the exudate (pus, mucus and blood).

3 Identification of protozoan and other parasites.

4 Bacteriologic examination for isolation and identification of enteric pathogens of the dysentery-enteritis-cholera group.

The bacteriologic examination is concerned principally with the isolation and identification of gram-negative intestinal bacilli, of which there are three important genera:

1 *Genus Salmonella*. The more important *Salmonella* types and the frequency of their isolation from man in the United States is shown in Table IV 2.

2 *Genus Shigella*. The dysentery bacilli of importance and most frequently encountered are:

S dysenteriae 1 (Shiga's bacillus, *S shigae*)
S schmitzii (*S dysenteriae* 2, *Shigella schmitzii*, *S ambigua*, etc.)

Table IV.2 Frequency of Salmonella Types from Man in the United States*

TYPES	GROUP	ANTIGENIC FORMULA	OLD NAME	PER CENT ISOLATED
S. typhimurium	B	I IV V XII 1 2 3	*B. pestis caviae* *S. aertrycke* Breslau bacillus	30 35
S. schottmuelleri	B	I IV V XII b 1 2	*B. paratyphosa* B *S. schottmuelleri* Paratyphoid B bacillus	20
S. typhosa	D	IX XII (Vi) d	*B. typhosa* *Eberthella typhosa* Typhoid bacillus	10 15
S. montevideo	C 1	VI VII g m s		
S. oranienburg	C 1	VI VII m t		
S. choleraesuis	C 1	VI VII 1 5	*B. suipestifer* *S. suipestifer* Hog cholera bacillus	5 10
S. newport	C-2	VI VIII e h 1 2 3		
S. derby	B	I VI XII f g		
S. bareilly	C-1	VI VII y 1 5		
S. enteritidis	D	I IX XII g m	*B. enteritidis* Gaertner bacillus	
S. panama	D	I IX XII e v 1 5 or 1 11		
S. give	E-1	III X e v 1 7		1 5
S. anatum	E 1	III X e h 1 6		
S. senftenberg	E-4	I III XIX g s t z27		

* Felsenfeld Am J Clin Path *15* 584 1945

S. flexneri 2a (Andrews and Inman W)
S. flexneri 3 (Andrews and Inman Z)
S. flexneri 4a (Boyd 103)
S. flexneri 6 (Boyd 88 Newcastle and Manchester bacilli)
S. boydii 2 (Boyd P 288)
S. boydii 7 (*S. etousae*, "Lavington" Type T)
S. sonnei (*S. ceylonensis* A)

3 *Tribe Escherichieae (Genus Escherichia)* Certain other gram negative bacilli of increasing importance in diarrheal disease are those coliform organisms that possess interrelationship with some of the *Shigella* types These have recently been placed in the Alkalescens Dispar group and are no longer included in the genus *Shigella* Classification is based on the antigenic relationship to *Escherichia coli* O groups as shown in Table IV 3

Table IV.3. The O Antigenic Schema for the Alkalescens-Dispar Group*

O GROUPS	O ANTIGEN	RELATIONSHIP TO *E coli* O GROUPS	EARLIER DESIGNATIONS
1	1a 1a 1b	Identical with 1a 1a 1b	*B alkalescens* or Alkalescens Type I
2	2	Strong relationship with 25 and other groups	Alkalescens Type II or *S tieté*
3	3	Strong relationship with 25 and other groups	*S ceylonensis* B or *S dispar* Type II or Alkalescens Type III (2 193)
4	4	Strong relationship with 4	*S madampensis* or *S dispar* Type I
5	5	Identical with 2a	None
6	*6*	*Identical with 9*	*S dispar Type III*
7	7	Identical with 7	None
8	8	Identical with 81	None

* From Frantzen (1950), and Ewing Taylor and Hucks (1950)

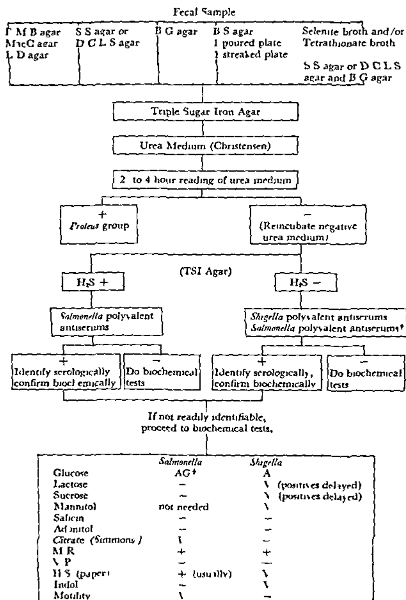
Differentiation of the pathogenic from the nonpathogenic enteric bacilli is based upon their behavior in lactose media Pathogenic organisms usually do not attack lactose, and when they do only after a considerable lapse of time Definitive identification is dependent on good initial isolation and careful selection of suspect colonies for detailed biochemical and serologic study Methods utilized for isolation and identification vary between laboratories Although there are numerous acceptable variations of the method outlined in Table IV 4 it may be employed as a useful guide

The expeditious laboratory diagnosis of communicable diseases occurring epidemically has become a matter of increasing importance For example, epidemics of dysentery may be unprecedented in size and the wartime experiences of the armed forces have emphasized the pressing need for acceleration in the diagnosis of enteric infections

Investigations of epidemic or sporadic outbreaks of bacillary dysentery, infantile diarrhea typhoid and paratyphoid fevers are complicated by the slowness of the usual bacteriologic procedures and the complexity of conventional identification systems Indeed more recent knowledge of the biochemical and serologic characteristics of the enteric pathogens has served to increase the time required for the conventional diagnostic methods used to characterize them In effect the old and sometimes superfluous techniques continue to be used along with the newer systems which could have at least partially replaced them

The paper disc–Petri dish culture method used in conjunction with a booster screening system offers an accurate and practical method for

Table IV.4. Outline of Procedure for Identification of *Salmonella* and *Shigella* Cultures*



	Salmonella	*Shigella*
Glucose	AG‡	A
Lactose	−	V (positives delayed)
Sucrose	−	V (positives delayed)
Mannitol	not needed	V
Salicin	−	−
Adonitol	−	−
Citrate (Simmons)	V	−
M R	+	+
V P	−	−
H₂S (paper)	+ (usually)	V
Indol	−	V
Motility	V	−

* From Edwards and Ewing A Manual for Enteric Bacteriology, CDC, February, 1952

† Occasional *Salmonella* cultures may fail to produce hydrogen sulfide in TSI agar Also certain salmonellae and shigellae cross agglutinate (see text) *Salmonella typhosa* and *Salmonella gallinarum* are anaerogenic Rarely anaerogenic cultures of other types appear

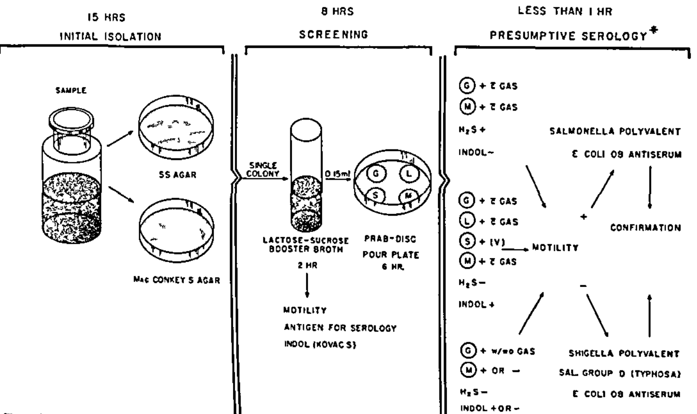


Figure IV 1 Outline of simplified procedure for identification of enteric pathogens using paper discs.**
* Glucose attacked with formation of acid and gas mannitol attacked with formation of acid and gas hydrogen sulfide formed indol not formed (See Fig IV 2 for configuration)
** From Sanders Faber and Cook Applied Microbiology 5 36 1957

Table IV.5. A Comparison of Biochemical Reactions Obtained by Paper Disc Petri Dish Technique with Conventional Kligler's Iron Agar Reactions**

Organism	Paper disc–petri dish tests: Glucose	Lactose	Sucrose	Mannitol	H_2S	Kligler/iron agar control tests
Salmonella						
typhimurium	AG/AG*	−/−	−/−	AG/AG	+/+	−/AG +
typhosa	A/A	−	−	A/A	+/+	−/A +
Shigella						
dysenteriae	A/A	−	−	−/−	−/−	−/A −
flexneri	A/A	−		A/A	−	−/A −
flexneri 6	AG/AG	−	−	AG/AG	/−	A/AG −
Escherichia coli 055	AG/AG	AG/AG	AG/AG	AG/AG	−	A/AG −
Alkalescens Dispar O1	A/A	−/−	−/−	A/A	−	−/A −
Proteus						
morganii	A/A	−/−	−/−	−/−	−/−	−/A −
vulgaris	AG/AG	−	AG/AG	−/−	+/+	+/AG +
Alcaligenes faecalis	−/−	−	−/−	−/−	−/−	−/−
Pseudomonas aeruginosa	−/−	−	−	−/−	−/−	−/−

* AG/AG: Acid and gas reactions recorded at 6 and 24 hr, respectively. A/AG: Acid reaction recorded at 6 hr, acid and gas. H_2S positive at 24 hr.
** From Sanders, Faber and Cook, Applied Microbiology 5:39, 1957.

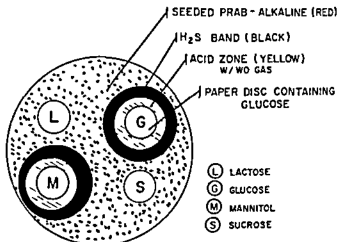


Figure IV 2 Configuration of paper disc Petri dish culture reactions *
* From Sanders Faber and Cook Applied Microbiology 5 39 1957

cultural differentiation of enteric pathogens in a short time The basic medium (phenol agar base) containing sodium thiosulfate and ammonium ferrous sulfate used in conjunction with a set of four carbohydrate discs* constitute a simple and expeditious diagnostic system As shown in Figure IV 1, the isolation identification procedure is divided into three phases initial plating screening and presumptive serology A configuration of the paper disc–Petri dish culture reactions is shown in Figure IV 2 Typical reactions of various enteric microorganisms obtained by this method and their excellent correlation with the results observed in standard Kliger's iron agar are shown in Table IV 5

Use of this paper disc–Petri dish technique provides for complete isolation and identification of enteric pathogens in less than 24 hours after receipt of fecal sample (see pages 837–838)

21

Bacillary Dysentery—Shigellosis

Definition. Bacillary dysentery is an acute or chronic inflammatory disease of the colon and occasionally involves the distal ileum It is

* May be obtained from Baltimore Biological Laboratories Inc Baltimore 18 Md

caused by members of the genus *Shigella* the dysentery bacilli and is characterized pathologically by inflammation and necrosis of the mucosa of the colon most marked in the distal portions Clinically its features are fever abdominal pain tenesmus and diarrhea with stools containing gross or microscopic blood and pus

Distribution The disease is widely distributed throughout the world the virulent infections by *Shigella dysenteriae*, the Shiga bacillus are more commonly seen in the tropics and the subtropics than in the temperate zone

Etiology The genus *Shigella* includes a variety of bacilli which vary among themselves in antigenicity and pathogenicity *Shigella dysenteriae* Shigas bacillus is highly toxic It has been responsible for severe epidemic outbreaks and is more often present in the tropics and subtropics The other members of the genus are not endotoxin producers and are generally somewhat less pathogenic causing less serious disease and a lower incidence of chronic dysentery

Epidemiology The disease is most prevalent wherever local conditions permit the contamination of food and water by the feces of infected individuals Carriers of the bacilli are not uncommon especially when the disease is prevalent The most important means of transmission are contamination of food by infected foodhandlers the transfer of the bacilli by houseflies and fecal pollution of water supply

The organisms are easily killed by chemical agents and direct sunlight They survive however for considerable periods in water ice and the mucoid discharges of active cases There are few diseases where the risk of infection to individuals caring for the patient is so great since

occurrence of mild "missed cases In the presence of an epidemic positive cultures may be obtained from as many as 25 per cent of apparently healthy contacts About 3 per cent of recovered cases become carriers of the organisms for shorter or longer periods of time These individuals are often difficult to identify because the bacilli are present only irregularly in the feces The agglutination reaction is not a dependable means for the identification of infected individuals since false positives and negatives and marked variations of titer in the same individual are common

Pathology The pathologic findings of bacillary dysentery are essentially an acute diffuse inflammation of the mucosa of the colon with the formation of a diphtheritic membrane followed by necrosis and ulceration (Figs IV 3 IV 4) This process is reflected by the presence of an inflammatory cellular exudate in the patients stool

In the early stage there is a rapidly spreading hyperemia of the mucosa often accentuated in the lymph nodules followed by edema hemorrhage and infiltration with granular leukocytes and macrophages This process frequently extends into the submucosa producing marked phlegmon like thickening of the intestinal wall The necrosis and desquamation of the epithelium with the formation of a diphtheritic type of membrane on the surface are followed by ulceration beginning on the



Figure IV 3



Figure IV 4

Figure IV 3 Colon of acu e bacillary dysen ery d phthe c membrane th ckening of wall

Figure IV 4 Diphtheritic membrane on surface and phlegmonous th ckening of the submucosa

summits of the intestinal folds and often extending deep into the submucosa and sometimes into the muscularis (Fig IV 5)

Th s process is usually not un formly distr buted tl roughout the colon tend ng to be most acute in the distal portion It may involve the lower ileum Perforation is rare With development of the ulcerated



Figure IV 5 Colon of acute bacillary dysentery stage of sloughing and beginning ulceration



Figure IV 6 Colon of chronic bacillary dysentery showing fibrosis and distortion of gland tubules.

Figure IV 7

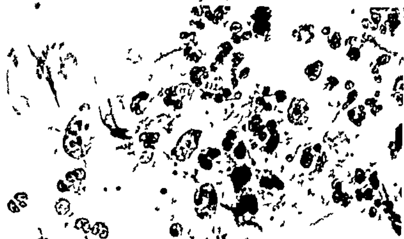




Figure IV 8

Figure IV 7 Early exudate in stool showing polymorphonuclear leukocytes and macrophage cells one of which resembles an ameba with extruded pseudopod.

Figure IV 8 Exudate in stage of ulceration macrophage cells and many polymorphonuclear leukocytes and erythrocytes

lesions secondary bacterial infection occurs and may participate importantly especially in a subsequent chronic stage of the disease

In cases of long duration adjacent ulcers may be connected by ulcerating channels beneath bridges of more or less hyperplastic mucosa In chronic recurrent cases there is much fibrosis of the mucosa and submucosa the epithelium losing its normal glandular structure Epithelial cystlike structures may be formed in the mucosa as the result of imperfect healing These mucus retention cysts have been found to retain the bacilli and they may be responsible for the intermittent discharge of organisms so characteristic of the chronic carrier state (Fig IV 6)

Clinical Characteristics The incubation period of the disease may vary from 24 hours to a week or more In the early stages of an outbreak cases may appear to be mild and to be merely instances of simple diar

rhea Certain of these, however, may suddenly be transformed into the acute or even fulminant types of the disease Variations in severity have led to the classification of cases into the following *clinical types*

1 Mild or catarrhal dysentery
2 Acute dysentery
3 Fulminant dysentery
4 Relapsing dysentery
5 Chronic dysentery

In the usual case the onset is abrupt and accompanied by fever which may reach 104° F Diarrhea appears promptly and the stools may number from 20 to 40 in 24 hours The evacuations at first feculent contain increasing amounts of blood and mucus and in the fully developed severe form of the disease may ultimately consist only of frequently evacuated small masses of sticky gelatinous bloodstained mucus which contain the characteristic cellular exudate and enormous numbers of the dysentery bacilli Abdominal pain may be severe and the evacuations involuntary and accompanied by intense tenesmus

Proctoscopic examination reveals a swollen diffusely inflamed mucosa often largely covered with mucopus When this exudate is removed the mucous membrane underlying it presents a somewhat granular surface which oozes blood freely Gross ulceration may be present When present the ulcers are usually shallow irregular in size and shape and covered with purulent exudate

In the fulminating type of the disease collapse is not uncommon and the abrupt onset may be accompanied by chill high fever and vomiting followed shortly by falling temperature profound toxemia and death

In mild cases the stools may remain feculent throughout and may contain gross blood and mucus Even in the mildest cases however microscopic examination of the feces will reveal the characteristic cellular exudate composed of red corpuscles many polymorphonuclear leukocytes and varying numbers of macrophage cells The latter may contain erythrocytes and cell debris and be suggestive of nonmotile forms of *Entamoeba histolytica* This possible confusion however, is eliminated by the examination of stained smears since the cell nuclei usually have degenerated and do not resemble those of the ameba (Figs IV 7 IV 8)

Prior to the advent of sulfonamide therapy the average mortality from acute bacillary dysentery was from 4 to 5 per cent Under epidemic conditions when the Shiga bacillus was the responsible organism the mortality has been as high as 50 per cent

Acute Bacillary Dysentery

Diagnosis The diagnosis of acute bacillary dysentery is based upon the demonstration of an inflammatory cellular exudate in the stools the characteristic appearance of the mucous membrane as seen through the proctoscope and recovery of the dysentery bacilli The agglutination reaction is of no use for early diagnosis and is not dependable in later cases The white blood cell count varies from normal to 15 000 or higher with elevation of polymorphonuclear elements

Treatment Experience with acute bacillary dysentery during World War II and more recently in Korea has led to material changes in treatment These are the result of accumulated observations of the limitations of the sulfonamide drugs and evaluation of the antibiotics as specific therapeutic agents There are three primary indications

1 Early and intensive specific antibiotic or chemotherapy
2 Correction and prevention of dehydration
3 *Control of toxemia*

1 *Specific Therapy* Eradication of *Shigella* infection is best accomplished by the use of oxytetracycline (Terramycin) tetracycline (Achromycin) chlortetracycline (Aureomycin) or chloramphenicol (Chloromycetin) Relatively small amounts administered within 24 hours have given as good results as larger doses administered over a longer period These antibiotic agents appear to be equally effective against the various types of *Shigella* The recommended dosage of each of these antibiotics is as follows

Initial dose 2 0 grams subsequent doses 1 0 gram after 12 and 24 hours

On this regimen almost all cases become bacteriologically negative before the seventh day Sigmoidoscopic examination reveals that the active colitis is controlled within four to five days and symptoms are brought under control with equal rapidity

Prior to the introduction of the antibiotic agents sulfonamide therapy had been demonstrated to be the most effective method of treatment However certain strains of *Shigella* notably of *S sonnei* showed relatively high initial resistance to these drugs Furthermore drug resistant strains of various types were encountered with increasing frequency especially when large numbers of patients were treated with insufficient amounts and when these drugs were used for mass prophylaxis The sulfonamide drugs have now been relegated to second place as therapeutic agents When they are used their effectiveness should be controlled by in vitro sensitivity tests and in the presence of resistant strains treatment with one of the antibiotics should be substituted

Sulfonamide therapy must be instituted early and must be intensive if optimal results are to be obtained It should be continued until clinical recovery has been achieved—until the stools no longer contain an inflammatory exudate stool cultures are negative and proctoscopic examination and x ray examination of the colon demonstrate complete healing

The soluble sulfonamides sulfadiazine and sulfathiazole are considered to be more effective than the insoluble compounds sulfaguanidine and Sulfasuxidine In the hot countries however, the former must be used with caution and with strict attention to the urinary output because of the hazard of renal tubular obstruction Fluid intake must be adjusted to yield a minimal urine output of 1500 ml each 24 hours if renal complications are to be avoided Maintenance of an alkaline urine during the period of sulfonamide therapy has been recommended as an auxiliary

if an ade

ore admin

retion and

thereb re l ce the effectiveness of the drug

The sulfonamide drugs of choice in the order of effectiveness and the recommended dosages are as follows

Sulfadiazine initial dose 2 0 grams 1 0 gram every six hours thereafter

Sulfathiazole initial dose 2 0 grams 1 0 gram every six hours thereafter

Sulfaguanidine 5 0 grams every six hours

Sulfasuxidine 5 0 grams every six hours

2 *Control of Dehydration* Dehydration and disturbance of electrolyte balance may occur rapidly in acute cases and may be severe especially in infants and in the hot tropics A large fluid intake should be instituted early and maintained at a level sufficient to insure a daily urine output in excess of 1500 ml Electrolyte replacement therapy is frequently essential in the severe cases

3 *Control of Toxemia* In most instances the toxemia may be controlled by adequate administration of fluids

Polyvalent antisera are of little if any value In the rare severe cases of infection by *S dysenteriae* (Shiga s bacillus) specific monovalent antiserum may have a temporary beneficial effect Such sera however are neither bactericidal nor bacteriostatic It is doubtful if antisera have a place in the treatment of bacillary dysentery especially when the rapidly acting antibiotic agents are immediately available

If an antiserum is to be used however the patient must invariably be tested for sensitivity The dose should be from 40 to 80 ml diluted in 500 ml of physiologic saline solution and given intravenously in severe cases or intramuscularly in less fulminant cases twice daily until the desired therapeutic effect is obtained The antitoxic action of adequate dosage of serum usually becomes evident within a few hours

The general measures of treatment include strict bed rest an easily assimilated diet rich in protein and vitamins and administration of sedatives as required If sulfonamide therapy is to be used daily administration of small doses of a mild saline cathartic should be begun early in the acute stage of the disease and continued until a cure has been attained This prevents injury to the inflamed mucous membrane

However if healing is incomplete and sigmoidoscopic examination reveals a persisting inflammatory reaction the cathartic should be instituted to protect the mucosa from mechanical trauma

Chronic Bacillary Dysentery

Pathology Chronic bacillary dysentery is characterized pathologically by scarring of the colon indolent ulceration and a continued subacute or chronic inflammation which periodically becomes acute The dysentery bacilli in many instances are no longer demonstrable and there is extensive secondary infection by other intestinal bacteria which appear to play an important role in the maintenance of the active pathologic process

It is said that approximately 25 per cent of the acute bacillary dysenteries among the British troops in the first World War became chronic with persisting disability Although the extensive use of sulfonamide therapy during World War II greatly diminished the incidence of the chronic disease it has not been eliminated However the greater effectiveness of the antibiotics and the rapid healing which accompanies their use should materially reduce the prevalence of chronic bacillary dysentery when specific treatment is instituted early

Clinical Characteristics The chronic forms of the disease are usually characterized by *successive periods of exacerbation and remission* Both clinically and pathologically they differ little if at all from certain types of so called idiopathic ulcerative colitis The periods of active disease are accompanied by fever and diarrhea with varying amounts of blood mucus and the characteristic cellular exudate in the stools Macrophages however may be rare Each period of activity contributes still further to the extensive scarring and fibrosis of the colon

A variety of factors appears to contribute to the disease In many instances there is disturbance of normal motor function with undue retention in the right half of the colon Primary and secondary nutritional *deficiencies are common and important In many instances these are due* to restriction of diet and in others to the inability of the patient to take sufficient amounts of protective foods A significant proportion of these patients appear to develop sensitization of the colon to particular food stuffs notably milk and inclusion of the particular food in the diet is followed by continued activity of the disease or even by its increased severity It appears probable likewise that there is a similar sensitization to certain bacterial proteins These factors together with the extensive and varied secondary bacterial infection complicate clinical management and greatly affect the prognosis

Treatment *The treatment of chronic bacillary dysentery is* commonly difficult and must be varied to meet the indications in the particular individual Dietary management is especially important Possible harmful effects of roughage have been overemphasized and have led to dietary restrictions that have produced serious secondary malnutrition

Antibacterial therapy using the sulfonamides Terramycin Aureomycin or Chloromycetin may be important The antibiotics however should not be administered over long periods because of their effect on the normal intestinal bacterial flora and the hazard of establishing a secondary *Candida albicans* infection

There is commonly a functional disturbance of the colon with stasis on the right side which tends to increase symptoms In most instances this is easily controlled by the daily administration of small amounts of sodium sulfate The possible role of sensitization to particular foods must be kept in mind Skin tests are useless for the identification of this complication and reliance must be placed entirely on the use of test diets

Prophylaxis of Bacillary Dysentery

In the prophylaxis of bacillary dysentery particular precautions must be taken with respect to the isolation of patients and to the sterilization

of bedding clothing and other articles which have been in contact with them Adequate disinfection and disposal of the stools are essential Control of food handlers the establishment of clean water and milk supplies sanitary sewage disposal and the elimination of flies are of fundamental importance The sequence of feces to flies or fingers to mouth must be interrupted

Ice manufactured from untreated water is an important factor in the transmission of the pathogenic intestinal bacteria

In areas where a safe water supply is not available all drinking water should be boiled Under field conditions chemical sterilization is reasonably effective for small quantities For this purpose 1 drop of 7.5 per cent tincture of iodine should be added to each quart of water or two or more tablets 130 mgm each of Halazone (*p* sulfonedichloramido benzoic acid) with thorough shaking to insure solution Effective amounts of the latter impart a distinct odor and taste of chlorine to the water which after a contact period of 30 minutes may be removed by the addition of 35 mgm of sodium sulfite followed by thorough shaking

Under special conditions and for brief periods when the disease is

Similarly if the antibiotics are used for prophylactic purposes administration must be restricted to limited periods There is no effective vaccine

22

Food Poisoning

Revised by Paul D Ellner

Definition Food poisoning is an inclusive term used to define a symptom complex The usual types are characterized by acute gastroenteritis with sudden onset of vomiting or diarrhea or both and abdominal pain—in some instances with fever in others with prostration and shock The duration is variable and depends upon etiologic factors An attack is frequently followed by instability and irritability of the gastrointestinal tract in convalescence The general mortality is approximately 1 5 per cent

Distribution. The disease is protean occurring in epidemic outbreaks wherever groups of individuals are exposed to the factors responsible

Etiology. The causes of food poisoning fall into three categories

1. Foods contaminated with metallic or other poisons
2. Foods inherently toxic or poisonous
3. Foods contaminated with certain bacteria
   a. Infections, with or without intoxications
   b. Intoxications without infection

Table IV.6. Metallic Poisons

CHEMICAL	FOOD	SYMPTOMS	ONSET
Antimony	Foods cooked in gray enameled or galvanized utensils	Vomiting	Few minutes to 1 hour
Cadmium	Liquids prepared in cadmium plated refrigerator trays, pitchers and other utensils	Vomiting, abdominal cramps, diarrhea	15 to 30 minutes
Sodium cyanide	Used in cleaning silver	Weakness, coma, respiratory failure	Few minutes
Sodium fluoride	Roach powder mistaken for baking powder or soda or powdered milk	Vomiting, abdominal pain, diarrhea, convulsions, paresis	Few minutes to 2 hours
Zinc	Acid foods or drink (apples, lemonade) prepared in galvanized iron utensils	Astringent taste, pain in mouth and throat, gastric distress, vomiting, abdominal pain, diarrhea	Few minutes or symptoms may be delayed as in food infections

Table IV.7. Poisonous Foods

FOOD	CAUSE	SYMPTOMS	ONSET
Fish	Unknown—occurs in many regions	Abdominal cramps and nervous symptoms	Few minutes
Shellfish (mussels and clams)	Dinoflagellates, Pacific coast U S A	Numbness of lips, respiratory and motor paralysis	5–30 minutes
Fava bean (or inhalation of pollen)	"Favism"	Fever, anemia, hematuria, jaundice	Within 1 hour
Milk from cows which have eaten snakeroot	Trematol or "alkali poisoning" not destroyed by pasteurization	Vomiting, colic, constipation	Variable after repeated use
Mushrooms, toadstools, etc	Alkaloids from 80 species	Vomiting, colic, diarrhea, convulsions	6–15 hours
Rye	*Ergot—a parasitic fungus*	Gangrene of ears, toes, fingers, headache, convulsions, itching	Gradual after several meals
Water hemlock	Toxin from leaves and root	Vomiting, convulsions	1–2 hours
Raw sprouted potatoes	Toxin (solanin?)	Vomiting, diarrhea, disturbed vision	?
Rhubarb leaves	Oxalic acid	Vomiting, colic, diarrhea	2 hours

Table IV.8. Bacterial Food Poisoning*

DISEASE	AGENT	TYPE	SYMPTOMS	ONSET
Botulism	Exotoxin of *Clostridium botulinum*	Intoxication	Difficulty in swallowing double vision, aphonia, respiratory paralysis	18 hours to 3–4 days
Clostridium perfringens food poisoning	*Clostridium perfringens* enteropathogenic Type A	Infection?	Abdominal pain, diarrhea	8–20 hours
Staphylococcus food poisoning	Enterotoxin from staphylococci	Intoxication	Vomiting diarrhea, abdominal cramps, prostration	1–6 hours
Salmonella food poisoning	*S typhimurium S enteritidis S choleraesuis* etc	Infection intoxication	Abdominal pain chills, fever diarrhea, vomiting	7 72 hours
Streptococcus food poisoning	Lancefeld s groups A C D and G	Infection?	Nausea, colic diarrhea	5 18 hours

* Adapted from Dack, G M Food Poisoning, Chicago, University of Chicago Press, 1943

Foods contaminated with metallic poisons are relatively uncommon causes of food poisoning (Table IV 6)

A variety of substances used for human food may be inherently poisonous These include certain plants fruits, fish and shellfish The more common causes of this type of food poisoning are listed in Table IV 7 It is wise, however, to consult with the native population before eating unfamiliar foods

Contamination of food by bacteria is the most important cause of food poisoning Many of these organisms become established in the intestinal tract causing true infections Others in the course of proliferation within the food, form toxic substances, and the symptoms which result after ingestion are those of a true intoxication rather than infection "Ptomaines," which were formerly considered important in this latter group are now recognized to be nontoxic when taken by mouth The common groups of food poisoning due to bacterial agents appear in Table IV 8

The bacterial type of food poisoning is the one most commonly encountered and will be the only one considered in detail

Botulism

Botulism is a true intoxication produced by the exotoxin formed by *Clostridium botulinum* types A B and E These are anaerobic spore bearing bacilli widely distributed in soil A soluble toxin is produced which is inactivated by boiling for ten minutes The spores, however, are extremely resistant The organisms are proteolytic often but not invariably producing an offensive odor

This type of poisoning is acquired by the ingestion of contaminated canned or preserved foods in which bacterial proliferation and toxin formation have occurred Such foods exhibiting any indication of gas formation or change in appearance should be rejected without tasting since severe effects may follow the ingestion of even minute amounts

Botulism is characterized by an acute encephalitis and interference with the parasympathetic system leading particularly to cranial nerve palsies and respiratory paralysis The onset may occur as early as 18 hours after ingestion and death may result in four to eight days rarely earlier Recovery is probable if the individual survives the ninth day Aspiration pneumonia is frequent The mortality rate is 60 to 70 per cent Serum therapy should be used if serum is available

Staphylococcus Food Poisoning

Varieties of *Staphylococcus* usually hemolytic strains of *Staphylococcus aureus* produce an enterotoxin which is an important cause of food poisoning The toxin is thermostable and is not destroyed by boiling for 30 minutes nor by refrigeration for long periods Certain of the strains will proliferate at icebox temperatures others will grow in media having a salt content equivalent to that of the brine used in pickling hams (10 per cent sodium chloride plus 1 per cent potassium nitrate) Food contaminated with these organisms has no abnormal odor or taste

Epidemiology. The staphylococcus food poisonings in most instances are due to contamination of food by infected humans This may be by droplet infection from foci in the respiratory tract or by direct inoculation with exudate from cutaneous staphylococcus infections such as furunculosis and impetigo The foods most commonly involved in outbreaks of food poisoning due to these organisms are milk custard and cream filled pastries minced meat, cured and tenderized" hams and sandwiches and salads containing mayonnaise or cream

Clinical Characteristics The clinical response to this form of food poisoning is a true intoxication and not an infection The onset is usually abrupt and acute and occurs within six hours after ingestion The symptoms are characteristic consisting of severe epigastric pain accompanied by continuous and even projectile vomiting and retching In the severe cases there is blood in the vomitus Prostration shock and syncope are not uncommon diarrhea may occur No inflammatory exudate has been found in the stools Since this type of poisoning is the reaction to an enterotoxin which acts as a severe gastrointestinal irritant it is usually of short duration and terminates with elimination of the toxin and toxin containing food

Treatment Treatment is symptomatic In severe cases vomiting may produce marked dehydration and loss of chlorides which must be replaced by appropriate amounts of physiologic saline solution administered intravenously

Streptococcus Food Poisoning

Outbreaks of food poisoning rarely have been traced to contamination of food with species of *Streptococcus* especially strains of Lancefield s groups A C D and G

The epidemiology of these infections is similar to that of staphylo coccus poisoning No true toxin is formed The symptoms apparently are the result of actual infection of the intestinal tract. After a period of five to 12 hours there are nausea occasionally vomiting abdominal pain cramps and diarrhea

Treatment should include early purgation by repeated small doses of magnesium sulfate or sodium sulfate rest and a soft diet If there is evidence of continuing infection sulfonamide or antibiotic therapy should be considered

Salmonella Food Poisoning

The most common form of bacterial food poisoning is that produced by certain members of the genus *Salmonella* These organisms are com monly parasites of animals and birds and frequently infect rats and mice *Salmonella* food poisoning in man may be the expression of a true in toxication produced by food that contains products of the bacilli but no viable organisms In other instances ingestion of food containing viable organisms is followed by actual infection of the intestinal tract The re sulting enteritis is usually of shorter duration than that produced by the *Shigella* It is commonly self limited and usually terminates without a prolonged carrier state Occasionally however chronic infection occurs with persisting ulceration of the colon

Etiology The organisms most commonly encountered and their hosts are

SALMONELLA SPECIES	HOSTS
S typhimurium	Warm blooded animals
S enteritidis	Domestic and wild animals especially rodents
S choleraesuis	Hogs
S schottmuelleri	Man
S paratyphi	Man

Epidemiology Rats and mice are naturally subject to outbreaks of *Salmonella* infection and when these rodents have access to human food contamination by their urine and feces may occur Larger mam mals are often infected with *S enteritidis* *S typhimurium* or *S choler aesuis* Ingestion of meat from such infected animals is productive of disease in man This is one of the important reasons for antemortem in spection of meat

Unpasteurized milk and cheese are likewise common vehicles of this group of organisms and the houseflies having access to *Salmonella*-con taining material may transmit them to human food In other instances symptomless or relatively healthy human carriers working as food han dlers may be responsible for outbreaks

The foods most commonly found to be sources of outbreaks of *Salmonella* food poisoning have been made up meats (*S enteritidis*) sausage (*S cholerasuis*) or salami meat sandwiches milk and milk products mayonnaise and mixed salads especially chicken salad (*S typhimurium*) and smoked or pickled fish

Outbreaks are usually explosive in character affecting all or nearly all individuals who have partaken of the contaminated food This characteristic is an important feature in the differentiation of food poisoning from infections by the *Shigella*

Clinical Characteristics. The incubation period is variable since the *Salmonella* may produce poisoning without infection or may produce true infection of the intestinal tract In the former instance symptoms occur within a few hours after ingestion of the contaminated food When the syndrome is the expression of active infection however it is more prolonged and the clinical phenomena likewise are of longer duration

In the majority of instances after an interval of 6 to 72 hours violent diarrhea occurs often accompanied by incontinence severe cramps and tenesmus In the presence of active infection examination of the stools in most instances will yield the causative organism and microscopic study will demonstrate the presence of erythrocytes polymorphonuclear leukocytes and macrophages Nausea and vomiting may occur In the more acute forms fever may be present and there may be considerable prostration The acute stage of food poisoning due to *Salmonella* infection cannot be distinguished clinically from infections by the *Shigella*

Salmonella food poisoning due to ingestion of bacterial products without infection may present the same symptoms Both the incubation period and the duration of the clinical phenomena tend to be shorter cultures are negative, and an inflammatory exudate is not observed in the stools

Treatment Treatment should include purgation with magnesium sulfate or sodium sulfate provided the patient is seen in the early stages of the attack If on the other hand severe diarrhea has persisted for two or three days purgation is of doubtful value If the episode is accompanied by vomiting the administration of parenteral fluids may be necessary In cases of established infection one of the sulfonamide drugs may be useful although these are less effective against *Salmonella* than against *Shigella* The antibiotics including Aureomycin Chloromycetin and Terramycin likewise frequently fail to modify significantly the course of the infection

Clostridium Perfringens Food Poisoning

Clostridium perfringens long associated with gas gangrene and other necrotizing wound infections has been shown to be definitely associated with a distinct form of food poisoning Enteropathogenic strains of *C*

perfringens differ from classic Type A strains antigenically in that the spores of the former strains are exceptionally heat resistant Although

pure cultures of these strains to human volunteers has produced the disease syndrome The importance of this form of food poisoning cannot be accurately determined since many laboratories investigating epidemics of food poisoning fail to include anaerobic cultures of suspected material However in laboratories employing anaerobic techniques, *C perfringens* has accounted for about 5 per cent of all food poisoning epidemics investigated

Epidemiology Enteropathogenic strains of *C perfringens* frequently occur in the feces of pigs cattle rats and mice as well as in sewage The organisms are rarely found in normal human stools (in contrast to the frequent occurrence of classic Type A strains) but are commonly isolated from blowflies Most outbreaks are associated with the ingestion of meat dishes that have been cooked the previous day cooled slowly to room or refrigerator temperature and heated immediately before serving The organism may be isolated from suspected foods as well as from the stools of patients provided anaerobic procedures are used

Clinical Characteristics Following an incubation period of eight to 20 hours patients develop acute abdominal pain and diarrhea Chills fever and headache or other symptoms of infection are not usually present The symptoms last for one day or less and spontaneous recovery is the rule It is believed however that fatal cases may occur among elderly or debilitated patients

Treatment Treatment is entirely supportive and symptomatic Bed rest is indicated as is the maintenance of an adequate fluid intake to prevent dehydration Kaolin and pectin or bismuth and pepsin preparations alone or combined with paregoric may be helpful in controlling the diarrhea

Diagnosis and Prophylaxis of Food Poisoning

Diagnosis The occurrence of food poisoning should be suspected when several individuals are seized with acute symptoms within a few hours to a day or two after having had a meal in common In the investigation of such outbreaks early study is of the utmost urgency

A list should be prepared of all the foods served and specific information obtained from every individual as to which of the foods were taken It is important to bear in mind however that such tabular investigation will often fail to identify clearly the offending food

Foods which are under suspicion should be obtained for bacteriologic examination and similarly cultures should be made of the vomitus stools and blood of each patient during the acute phase

Prophylaxis The prevention of the bacterial types of food poisoning is dependent upon proper methods for the storage of food satisfactory sanitation of the kitchen and icebox sterilization of kitchen utensils

and tableware, and inspection of food handlers It is particularly important that rats, mice and flies be prevented from gaining access to human food

Such products as sausage and tenderized hams should be thoroughly cooked Dishes prepared some hours in advance of the meal at which they are to be served must be stored at low temperatures in efficient iceboxes Foods which are apt to become contaminated and have been incriminated frequently as causes of food poisoning such as meat sandwiches or potato salad, should not be held at room temperature for more than three hours prior to consumption

Kitchen personnel should be inspected for the presence of staphylococcus or streptococcus infections of the skin Infected personnel must be eliminated from the kitchen until the lesions have healed Intestinal disturbances among food handlers must be reported and investigated promptly by appropriate bacteriologic techniques Individuals infected with pathogenic organisms commonly transmitted by food or drink should not be employed in the preparation or serving of food Proper attention to these measures will afford relatively great protection

23

Cholera

Synonyms. Asiatic cholera, Indian cholera

Definition. Asiatic cholera is an acute infectious disease caused by *Vibrio comma* and characterized by profuse and purging diarrhea, vomiting, extreme dehydration, muscle cramps, suppression of urine, collapse and, in a high proportion of untreated cases death The organism is present in the intestine and in the rice water stools during the acute stage It multiplies especially in the small intestine and, undergoing lysis, liberates an endotoxin which is responsible for desquamation of the superficial epithelium of the mucosa and for other toxic manifestations of the disease

Distribution. The disease is widely endemic in Asia and the Far East Most of the pandemics have originated in India, especially on the delta of the Ganges River, which is the important persisting focus There is scarcely a country of the world that has not at some time been visited by cholera In recent years the most important outbreaks outside India and China have been in Russia and the Ukraine, except for a severe epidemic in Egypt in 1947 with some 21,000 cases and a death rate of approximately 50 per cent

The present major endemic centers are the Ganges Delta in lower Bengal, and in China the Yuan River valley Hunan in the upper

trillum cholerae) the
n appearing S shaped
owing to end to-end attachment of two vibrios It possesses a long terminal flagellum it is gram negative and actively motile

Cultural Characteristics The vibrio is strictly aerobic growing readily on ordinary media having a *p*H from 7 0 to 9 0 Growth is inhibited by moderate acidity A typical strain exhibits significant characteristics in culture The more important include liquefaction of gelatin and coagulated blood serum production of indole and reduction of nitrates to nitrites which is responsible for the cholera red reaction Glucose maltose and saccharose are fermented without the formation of gas xylose and arabinose are not fermented and fermentation of lactose is absent or late

Vibrio comma has little resistance to disinfecting agents or to drying It is rapidly overgrown by other organisms and is not long demonstrable in water heavily contaminated with sewage In ordinary river water however it will survive for one to two weeks and for as long as a month in spring water The organisms remain viable in stools for one to two days in summer and up to a week in cold weather

Different strains of the organism vary widely in colony morphology in motility and in biochemical activity Final identification depends therefore upon agglutination in specific monovalent O antigen serum

Numerous other free living vibrios inhabiting water have been found in man These may exhibit the same staining and cultural characteristics as the true *V comma* Moreover nonagglutinating strains are commonly found in man in endemic areas during interepidemic periods Their significance is uncertain

Epidemiology Infection is acquired by ingestion of *V comma* with food or drink The reservoir consists of healthy carriers infected individuals during the incubation period and patients with mild or acute disease In the presence of outbreaks 1 to 10 per cent of the healthy population of the area may be carriers The period of excretion of vibrios by such individuals usually does not persist beyond seven to ten days but may continue for three weeks to two months In general it is said 97 per cent of carriers become vibrio free within one month The organisms are seldom excreted in the feces of acute cases for more than seven to ten days and often for lesser periods

Spread of the disease as in the great pandemics has always taken place along trade routes Pilgrimages have frequently been intimately related to epidemic outbreaks and wide extension of the disease Local dissemination down the river valleys commonly occurs in endemic areas probably as a result of the contamination of water Circumscribed outbreaks are associated with contaminated water supply and food and with exposure to fomites

In the endemic regions climatic influences seem to be important In India most epidemics have been preceded by failure of the rains In

Bengal the maximal incidence is in the hot dry months from March to June when the water supply is most limited and presumably most highly contaminated In other areas epidemics not uncommonly follow sudden heavy rains and floods with their dispersal of human excreta

In towns and cities two types of outbreaks due to water transmission occur When the general water supply is contaminated the outbreak is widespread and explosive When on the other hand it originates from contamination of isolated wells the cases are local or sporadic

Contamination of food is an important factor in transmission Food handled by infected persons is dangerous so also is the ingestion of uncooked foods vegetables and salads especially lettuce and celery which have been fertilized with night soil or freshened with contaminated water Milk is a common vehicle The widespread practice in the Orient of eating uncooked or lightly cooked shellfish and fish also provides a ready means of transmission Flies and cockroaches may be important vectors Although the vibrios are usually rapidly destroyed in the flys gut they may be recovered from the insects feces for two to 12 hours

Pathology The pathologic process of cholera is essentially an acute intestinal intoxication leading to profound dehydration and chemical imbalance within the body A severe or fatal toxic nephritis with little organic change may occur The histopathology resembles that of a non specific enteritis the villi are not denuded Vibrios are rarely found deeper than the superficial layer of epithelium

In fatal cases the prominent findings are early rigor mortis and extreme shrinkage and dryness of the tissues evidenced particularly by the shrunken face and eyeballs and "washerwomans" fingers The subcutaneous tissue and muscles are dry the peritoneum is dry sticky and dull with the exception of the layer covering the ileum which is usually congested The spleen is small and dry The lumen of the intestine may be filled with the characteristic rice water transudate

The serious manifestations of the disease are found through laboratory tests Loss of fluids is extreme electrolytes are also depleted with relatively great loss of base and consequent diminution of the alkali reserve The sodium chloride loss may exceed 50 grams in 24 hours The specific gravity of the blood may be increased from a normal of 1 056-1 058 to above 1 070 Concentration of the blood is further indicated by high values for the red cell count and hemoglobin percentage

The degrees of salt and water depletion vary in different cases and at different stages of the disease Although both exist in most cases and both are associated with dehydration their effects are somewhat antagonistic In predominant water depletion thirst is prominent and urine output reduced The sodium chloride and urea content of the blood are normal or elevated and the plasma volume normal until the late stages of dehydration

When salt depletion predominates thirst is absent the urine output remains normal until late and sodium chloride is absent from the urine The plasma chlorides are decreased the blood urea elevated and plasma volume decreased Vomiting and cramps occur the blood pressure falls progressively and shock develops from peripheral circulatory

failure These changes are accompanied by a pronounced and progressive acidosis which results from the accumulation of normal metabolic end products and the extreme loss of base In severe cases there may be complete suppression of urine followed by uremia and death

Clinical Characteristics The disease classically presents four clinical stages The stage of incubation lasting one to three or four days is the least definite and may be accompanied by mild or increasing diarrhea

The incubation period is followed by the stage of evacuation A typical attack as observed in epidemic outbreaks commonly presents an abrupt onset with the rapid development of progressive purging vomiting and muscle cramps

In severe infections this second phase is followed by an algid or collapse stage in which death commonly occurs In the event of survival the fourth stage that of reaction appears accompanied by rise of temperature and progressive lessening of symptoms

The stage of evacuation is dominated by purging vomiting muscle cramps and exhaustion The stools at first feculent soon present the appearance of "rice water and are passed without cramps or tenesmus Several liters of fluid may be lost in 24 hours Profuse continuous vomiting and retching and often uncontrollable hiccough appear early in the second stage The appearance of the patient changes rapidly owing to dehydration and progressive shrinking of the tissues especially of the face and the extremities The rectal temperature usually does not exceed 100° or 102° F

In serious cases after a period of two to 12 hours the patient passes into the algid stage or stage of collapse which may persist for a few hours to several days The purging and vomiting often cease and the clinical picture is essentially that of profound shock Muscle cramps commonly continue and are severe involving many muscle groups This stage is dominated by failure of the circulation with increasing tachycardia cyanosis and progressively falling blood pressure The body as a whole is shrunken the surface cold and the temperature usually below normal There is oliguria with albuminuria and in very severe cases anuria Consciousness is retained until the onset of terminal coma

In the stage of reaction acute symptoms disappear the stools become less liquid and their bile coloring returns In favorable cases recovery may occur within a week In others urinary secretion is not restored and progressive nephritis with rapidly increasing uremia may supervene in other instances a typhoidal state develops

In the presence of an epidemic of cholera a wide variety of clinical types may be encountered These vary from ambulatory cases with only mild gastrointestinal symptoms to the fulminating "cholera sicca" in which early death occurs without diarrhea or vomiting

Diagnosis When cholera is prevalent in an area all intestinal disturbances particularly those accompanied by diarrhea must be considered as possible instances of the disease The classic clinical picture is so characteristic that little difficulty should be encountered in its identification Microscopic examination of the colorless albuminous fluid

stools reveals epithelial and mononuclear cells and small flecks of mucus but no true inflammatory exudate The vibrios may likewise be seen

Definitive diagnosis is based upon recovery of *V comma* Selective media, such as alkaline nutrient agar, Aronson's, a modified Wilson and Riley's solid media, or Read's modification of Wilson and Blair's fluid enrichment medium, should be used for primary isolation Final identification of the organism must be based upon agglutination in specific antisera containing the somatic or "O" agglutinins

Treatment. Replacement of fluids and electrolytes is the most essential feature of the treatment of cholera Although certain sulfonamides, chloramphenicol (Chloromycetin) and oxytetracycline (Terramycin) cause rapid disappearance of the vibrios from the stools, they do not alter the clinical course nor significantly affect the mortality rate Plasma and whole blood are seldom necessary and may be very harmful They should be given only when specific indications exist

The blood pressure, pulse rate and volume, and the color and consistency of the blood and the urine output are dependable clinical indications of the amounts of fluids required Excess fluid is dangerous and is indicated clinically by palpitation, restlessness, chest pain, coughing and edema As the blood specific gravity approaches normal administration must be reduced or discontinued

Alkali deficit develops early, and severe acidosis is frequent Clinical appraisal is difficult the type and rate of respiration are not dependable guides, ketone bodies are not necessarily present in the urine in the acidosis of cholera However, tests for urine volume and acidity are helpful within limits The most accurate guides to the requirements for alkali are the pH, the carbon dioxide combining power and the urea content of the blood

Repeated determinations of blood specific gravity provide the most accurate control of fluid administration Roger's technique offers a simple method A series of solutions of glycerin and distilled water is used The specific gravities lie 0 002 apart from 1 050 to 1 070 (*i e*, 1 050 1 052, 1 054, etc) Ten to 15 ml of each solution is placed in individual small bottles A drop of blood is introduced into each container, the specific gravity of the blood is that of the solution in which the drop neither rises to the top nor sinks to the bottom

A newer method utilizes copper sulfate solutions, these expand with changes in temperature at the same rate as does blood thereby eliminating errors inherent in the glycerin technique

Fluids should be administered intravenously during the active stage and there should be no hesitation in cutting down on a vein and inserting an indwelling cannula Patients with cholera require relatively large amounts of fluid Intravenous therapy may be required for 48 hours The following fluids are recommended

1 *Physiologic saline solution*

In the less severe and uncomplicated cases, and in the absence of severe acidosis and collapse, physiologic saline solution may be adequate It may be necessary to administer 1000 ml every four hours as determined by the criteria for fluid requirements

2 Hypertonic saline solution

Sodium chloride	14 0 gm
Distilled water	1000 ml

3 Alkaline saline solution

Sodium chloride	6 0 gm
Sodium bicarbonate	18 0 gm
Distilled water	1000 ml.

This solution must not be sterilized by boiling or autoclaving since such procedures change the bicarbonate to the caustic carbonate The following technique may be utilized Dissolve the sodium chloride in distilled water and sterilize by boiling Remove from the heater and immediately add the sodium bicarbonate taken directly from the original container and weighed under sterile conditions The solution should be cooled to body temperature or slightly higher and used immediately

Replacement of Fluid and Electrolytes A total of 2000 ml of fluid should be given in the first two hours as follows 500 ml of alkaline saline solution followed by 1500 ml of physiologic saline solution It is desirable but not essential to add to this solution 75 grams of glucose and 3 mgm of thiamine hydrochloride

Thereafter, physiologic saline solution should be administered in amounts as indicated up to 1000 ml every three to four hours until the specific gravity of the blood approaches normal

Additional alkaline saline solution may be required to control the acidosis It must be given cautiously however with attention to avoidance of alkalosis It should be discontinued immediately when the urine becomes alkaline

Some clinicians consider that hypertonic saline solution in limited amounts is beneficial in early and more severe cases before marked dehydration has occurred

Specific Treatment Various of the sulfonamide drugs have been shown to eliminate the *V comma* from the stools in a relatively short time This does not appear to affect the clinical condition of the patient Those preparations which are absorbed and produce measurable blood levels are contraindicated because of the depressed renal function

The drug of choice is phthalylsulfacetimide (Thalamyd) Although this produces effective concentrations in the intestinal wall it is not absorbed into the blood stream There are no toxic effects Dosage 5 grams initially thereafter 1 gram every two hours for five days

Chloromycetin and Terramycin likewise cause rapid disappearance of the vibrios but do not affect the course of the disease

Nonspecific Treatment Absolute rest and quiet are essential Food should be withheld Even in the presence of thirst water should be given by mouth in only small amounts during the acute phase Small doses of morphine or even light intermittent anesthesia may be necessary for the relief of muscle cramps although these should not be used in the stage of collapse Severe vomiting may be partly controlled by oral administration of dilute solutions of cocaine 0 0075 gram per dose

Convalescence in severe cases may be delayed and after the acute stage there is usually a residual disturbance of the plasma proteins

Prognosis The average mortality in virulent epidemics of cholera is 50 to 60 per cent This may often be reduced to about 20 per cent in carefully treated patients

Prophylaxis Effective prophylaxis against cholera entails proper isolation of cases sterilization of bedding and other articles contaminated by the patient and disinfection and sanitary disposal of fomites Protection of water supply and sterilization of all water for human use avoidance of all uncooked foods and protection of food and drink against contamination by flies are essential

In the presence of an epidemic outbreak mass immunization should be carried out if practicable *Individuals entering endemic or epidemic areas should be immunized with an approved cholera vaccine* The recommended dosage with an interval of seven to ten days between injections is first dose 0 5 ml second dose 1 ml A stimulating dose of 1 ml should be administered every four to six months as long as danger of infection is present When cholera is epidemic this procedure should be supplemented by a full course of vaccine prepared from strains of immunogenic potency

Immunity is of short duration not exceeding four to six months and is much less effective than immunization against typhoid It appears that maximal immunity is attained about the tenth day after immunization

Chemoprophylaxis Preliminary observations with Thalamyd suggest that a daily dose of 0 2 gram has significant protective value and that it may prove useful for both individual and mass protection in the presence of epidemic conditions

24

Brucellosis

Revised by Paul D Ellner

Synonyms Undulant Malta Mediterranean Gibraltar rock Neapolitan or Cyprus fever Mediterranean phthisis melitensis septicemia abortus fever fievre caprine febris melitensis in the southwest United States Rio Grande fever slow fever goats milk fever

Definition *Brucellosis is a specific septicemia* of man and animals produced by *Brucella melitensis Br abortus* or *Br suis* It is characterized by prolonged disability asthenia and varied symptoms and may be acute or chronic *In its acute phase there is a remittent fever which may exhibit a series of relapses separated by brief apyrexial periods* The

chronic form is often associated with little or no fever and may o the absence of an antecedent acute phase The death rate of un or inadequately treated cases in different parts of the world varies to 5 per cent

Distribution. The genus *Brucella* occurs in naturally infected mals in all parts of the world and human brucellosis in consequence a cosmopolitan distribution The clinical types and the severity of disease will vary in different areas in accordance with the relative p ponderance of the three species of the genus in these regions

Etiology. Brucellosis is a disease primarily of animals the capri species *melitensis* occurring in goats the bovine or *abortus* species i cattle and the porcine or *suis* species in hogs In these animals the in fection is an important cause of abortion

The members of the genus *Brucella* are small gram negative non motile, nonsporeforming coccobacilli *Brucella melitensis* in culture ex hibits coccoid and bacillary forms depending upon the strain the age of the culture and the medium for cultivation, *Brucella abortus* exhibits less variation and usually appears as a stumpy rod *Brucella suis* com monly appears as a rodlike organism

Cultural Characteristics. These organisms do not grow well on ordinary laboratory media Primary blood stream isolations are not easily accomplished probably owing to the paucity of organisms in the cir culation Furthermore it has been demonstrated that certain peptones in the isolation media may be toxic to the *Brucella* organisms Once isolated however, the various strains grow well on ordinary laboratory media Trypticase soy broth or agar Albini *Brucella* media or liver infusion agar or liver infusion broth with a pH of 6 8 to 7 4 should be used especially for primary isolation Growth is slow requiring up to 14 days On solid media the colonies are small usually smooth and opaque In liquid media they produce diffuse turbidity

The *melitensis* and *suis* strains are aerobic For primary isolation and a varying number of subsequent generations the *abortus* strains require a carbon dioxide content 10 per cent by volume over that of atmospheric air Such increased carbon dioxide tension does not inhibit growth of *melitensis* or *suis*

Differentiation among the three species of the genus *Brucella* is diffi cult Antigenic analysis by the agglutinin absorption test is not satis factory Small absorbing doses must be used and these in turn must be adjusted to the titer of the serum at hand Furthermore, antigenic simi larities are such that the test will serve to distinguish only between *melitensis* on the one hand and *abortus* and *suis* on the other Serologic cultural correlations are at times variable Transitional types have been reported which do not conform to species identification by sero methods

Certain cultural characteristics however, are useful for tentative identification These are indicated in Table IV 9, *Brucella melitensis* does not require an increased carbon dioxide tension for primary isolation nor does it produce hydrogen sulfide Glucose is utilized in the medium, and growth is not inhibited by aniline dyes *Brucella abortus*, on the

Prognosis The average mortality in virulent epidemics of cholera is 50 to 60 per cent This may often be reduced to about 20 per cent in carefully treated patients

Prophylaxis Effective prophylaxis against cholera entails proper isolation of cases sterilization of bedding and other articles contaminated by the patient and disinfection and sanitary disposal of fomites Protection of water supply and sterilization of all water for human use avoidance of all uncooked foods and protection of food and drink against contamination by flies are essential

In the presence of an epidemic outbreak mass immunization should be carried out if practicable Individuals entering endemic or epidemic areas should be immunized with an approved cholera vaccine The recommended dosage with an interval of seven to ten days between injections is first dose, 0 5 ml second dose 1 ml A stimulating dose of 1 ml should be administered every four to six months as long as danger of infection is present When cholera is epidemic this procedure should be supplemented by a full course of vaccine prepared from strains of immunogenic potency

Immunity is of short duration not exceeding four to six months and is much less effective than immunization against typhoid It appears that maximal immunity is attained about the tenth day after immunization

Chemoprophylaxis Preliminary observations with Thalamyd suggest that a daily dose of 0 2 gram has significant protective value and that it may prove useful for both individual and mass protection in the presence of epidemic conditions

24

Brucellosis

Revised by Paul D Ellner

Synonyms Undulant Malta Mediterranean Gibraltar rock Neapolitan or Cyprus fever Mediterranean phthisis melitensis septicemia abortus fever fievre caprine febris melitensis in the southwest United States Rio Grande fever slow fever goats milk fever

Definition Brucellosis is a specific septicemia of man and animals produced by *Brucella melitensis Br abortus* or *Br suis* It is characterized by prolonged disability asthenia and varied symptoms and may be acute or chronic. In its acute phase there is a remittent fever which may exhibit a series of relapses separated by brief apyrexial periods The

chronic form is often associated with little or no fever and may occur in the absence of an antecedent acute phase The death rate of untreated or inadequately treated cases in different parts of the world varies from 2 to 5 per cent.

Distribution The genus *Brucella* occurs in naturally infected animals in all parts of the world and human brucellosis in consequence has a cosmopolitan distribution The clinical types and the severity of the disease will vary in different areas in accordance with the relative preponderance of the three species of the genus in these regions

Etiology Brucellosis is a disease primarily of animals the caprine species *melitensis* occurring in goats the bovine or *abortus* species in cattle and the porcine or *suis* species in hogs In these animals the infection is an important cause of abortion

The members of the genus *Brucella* are small gram negative nonmotile nonsporeforming coccobacilli *Brucella melitensis* in culture exhibits coccoid and bacillary forms depending upon the strain the age of the culture and the medium for cultivation *Brucella abortus* exhibits less variation and usually appears as a stumpy rod *Brucella suis* commonly appears as a rodlike organism

Cultural Characteristics. These organisms do not grow well on ordinary laboratory media Primary blood stream isolations are not easily accomplished probably owing to the paucity of organisms in the circulation Furthermore it has been demonstrated that certain peptones in the isolation media may be toxic to the *Brucella* organisms Once isolated however the various strains grow well on ordinary laboratory media

media the colonies are small usually smooth and opaque In liquid media they produce diffuse turbidity

The *melitensis* and *suis* strains are aerobic For primary isolation and a varying number of subsequent generations the *abortus* strains require a carbon dioxide content 10 per cent by volume over that of atmospheric air Such increased carbon dioxide tension does not inhibit growth of *melitensis* or *suis*

Differentiation among the three species of the genus *Brucella* is difficult Antigenic analysis by the agglutinin absorption test is not satisfactory Small absorbing doses must be used and these in turn must be adjusted to the titer of the serum at hand Furthermore antigenic similarities are such that the test will serve to distinguish only between *melitensis* on the one hand and *abortus* and *suis* on the other Serologic and cultural correlations are at times variable Transitional types have been reported which do not conform to species identification by serologic methods

Certain cultural characteristics however are useful for tentative identification These are indicated in Table IV 9 *Brucella melitensis* does not require an increased carbon dioxide tension for primary isolation nor does it produce hydrogen sulfide Glucose is utilized in the medium and growth is not inhibited by aniline dyes *Brucella abortus* on the other

Table IV 9 Differentiation of the Species of the Genus Brucella

	Requirement for CO_2	Production of H_2S				Utilization of mannose	Growth in dyes*	
		Days					Thionin 1:800	Basic fuchsin 1:200
		1	2	3	4			
B. melitensis	−	−	−	−	−	−	−	−
B. abortus	+†	3+	2+	1+	1+	+	+	−
B. suis	−	4+	4+	4+	4+	+	−	+

* Specified dilutions of dyes should be used to obtain differentiation. Use certified dyes and Bacto tryptose. This varies with different basic media. Dye tablets of the proper concentration are commercially available.
† Laboratory strains that have become aerobic do not require CO_2 for isolation from infected animals.
Adapted from Smith, D. T., et al.: Zinsser's Textbook of Bacteriology, 11th ed. New York: Appleton-Century-Crofts, Inc., 1957.

hand requires increased carbon dioxide concentration It produces varying amounts of hydrogen sulfide Glucose utilization is variable and growth is inhibited by thionine but not by methyl violet basic fuchsin or pyronine *Brucella suis* is aerobic and is a strong producer of hydrogen sulfide It utilizes glucose and growth is not inhibited by thionine but is inhibited by the other dyes

Epidemiology. The genus *Brucella* is widely distributed throughout the world and produces natural infections in horses fowl dogs sheep cattle goats wild deer and wild buffalo as well as man The human disease is acquired from direct or indirect contact with goats cattle or hogs The tissues and discharges of infected animals contain the organisms The *Brucella* are commonly present in the milk of infected cattle and goats

In animals which have aborted the organisms are present in large numbers in the vaginal discharges They are present less commonly in the urine and feces The frequent association of *Br abortus* with both fistulous withers and abortion of horses provides a source of potential infection for individuals in contact with such animals

The *Brucella* are not easily destroyed under natural conditions except by temperatures above 55° C or by exposure to direct sunlight They will survive in dry soil for 40 to 60 days in sterile tap water for 42 days in meat curing brine for 40 days and in milk at 10° C for ten days They have been reported to remain viable in unpasteurized cheese for periods up to two months

Man acquires the infection by ingestion of contaminated or infected food or drink possibly by inhalation of dust containing the organisms and by penetration of *Brucella* through the abraded or even unbroken skin and mucous membranes Unpasteurized milk or milk products are the commonest vehicles of human infection Since the disease in animals is a septicemia slaughterhouse workers meat handlers animal husbandry men and veterinarians are particularly exposed

In the past 25 years brucellosis has become an important public health problem In the United States the prevalence of the disease varies directly with the extent of the hog raising industry In other highly endemic areas it is observed particularly in connection with goat raising or where goats milk is commonly used as a beverage elsewhere it is sporadic In the United States it involves particularly young adult men especially

farmers packing house workers and veterinarians In Malta it is commonest in children under five years of age in whom it is usually relatively mild and often unnoticed

There is no evidence of transmission directly from man to man

It is probable that infection even if subclinical confers lasting immunity Although artificial immunization has proved of value in animal husbandry it has not been successfully applied to man

Pathology The organisms invade cells of the reticuloendothelial system producing granulomata which may undergo necrosis There is little phagocytic action These lesions occur in many tissues and organs especially the liver spleen and lymph nodes Less frequently they are found in the meninges and brain the male and female genitalia and the skin eyes and lungs Although there may be involvement of joints and long bones the commonest lesion in the osseous system is spondylitis of the lumbar spine with destruction of the intervertebral disk and the adjacent vertebral bodies Localization may occur on previously damaged heart valves causing subacute bacterial endocarditis

The blood shows a progressive microcytic anemia with leukopenia and relative lymphocytosis in which there may be an appreciable increase of immature small lymphocytes

Clinic

studies

and ave

The prolonged relapsing type of fever which gave rise originally to the term "undulant fever is much more commonly observed in *melitensis* infections (60 per cent of the cases in Malta) and the mortality rate in these infections is somewhat higher the undulant type of fever on the other hand is only occasionally seen in *abortus* and *suis* infections Three main types of disease are recognized on the basis of the temperature curves—the intermittent the undulant and the malignant

The incubation period varies from 3 to 21 days The procedures recommended for establishing the diagnosis are

1 Recovery of the organism by culture of blood excreta or spinal fluid

2 Agglutination reaction

The onset is usually gradual and insidious with generalized aching headache anorexia chilliness insomnia backache and stiffness or pain in the neck and various joints Constipation is usual and there is commonly a slowly progressive loss of weight As these symptoms develop elevation of temperature occurs in the afternoon or evening slowly increasing in degree and often accompanied by sensations of chilliness but rarely by frank chill As the disease becomes established a cough productive of small amounts of mucoid or mucopurulent sputum is not uncommon The fever appearing in the afternoon or evening commonly passes off during the night and is often accompanied by drenching sweats of such severity as to require change of bedclothing In the fully established case the temperature may reach 104° F or higher at night and be normal or under 100° F in the morning In most instances the febrile period persists for six weeks to several months terminating

slowly by lysis There is often marked disparity between the subjective sensations of the patient and his appearance on the one hand and the temperature record on the other

Physical examination usually reveals little or nothing other than some degree of splenomegaly hepatomegaly and lymphadenopathy especially of the cervical and axillary lymph nodes Even in the presence of considerable cough physical signs over the lungs are usually absent X ray examination however may demonstrate small areas of confluent lobular pneumonia Neurologic changes such as disturbances of reflex activity and gross tremors of the tongue and extended fingers are commonly noted

In the undulant type of brucellosis after return of the temperature to normal and a varying afebrile period a similar febrile phase recurs These waves of fever may be numerous and extend over a prolonged period

The malignant form of brucellosis is rare in the *Br abortus* and *Br suis* types of the disease When it occurs it is characterized by sudden onset and an acute course of high sustained fever with great prostration It is usually fatal

During the acute phase there may be hydrarthrosis and transient periarticular swellings Regional localizations are not unusual Involvement of the central nervous system may produce the symptoms and signs of acute encephalitis myelitis or meningitis These may be very transitory

Abdominal pain is common especially in the early stages of the disease and has frequently led to mistaken diagnosis and surgical intervention for a suspected acute appendicitis or acute cholecystitis Less commonly there may be epididymitis prostatitis seminal vesiculitis or oophoritis The infection may occasionally cause abortion In some instances there is a transient cutaneous eruption usually papular macular or maculopapular which may simulate the roseola of typhoid

Chronic Brucellosis Chronic brucellosis is protean in its phenomena Its definitive diagnosis is frec
toms or signs may be entirely lac
cent of such cases give a history
vidual suffering from this type of infection is often not entirely incapacitated The most striking clinical phenomena are physical and nervous weakness and exhaustion which may be accompanied by mild and usually unrecognized fever the temperature often not exceeding 100° F There are three cardinal features—weakness low grade fever and complete absence of other objective physical findings Peripheral neuritis is a frequent complication

Symptoms relating to the central nervous system are frequently observed and are usually evanescent These include headache vertigo nuchal rigidity aphasia psychic disturbances and even transitory paralysis In such instances the spinal fluid may exhibit increased pressure a slight increase in the cell count and albumin and a decrease of the globulin and sugar content

Diagnosis The diagnosis of brucellosis on clinical grounds alone is undependable and hazardous The protean manifestations of the disease

often produce difficult problems of differential diagnosis In many instances the clinical picture may resemble typhoid tuberculosis influenza or malaria In other instances it may be confused with acute appendicitis cholecystitis bronchitis pyelitis and even with Hodgkin's disease The chronic form is commonly confused with neurasthenia or psychasthenia

There are three important criteria for diagnosis

1 Recovery of the organism
2 An agglutination titer of 1/320 or higher
3 Lower initial titer followed by a rising titer

Recovery of the organism constitutes the only absolute confirmation of diagnosis Present techniques permit recovery of *Brucella* from venous blood in a high proportion of cases during the initial acute phase or during exacerbation These techniques are superior to guinea pig inoculation However repeated cultures may be necessary It is recommended that no more than 2 to 3 ml be used as inoculum because of the possible presence of inhibiting substances in the blood

The initial culture should be made in trypticase soy broth and Albimi *Brucella* medium Subcultures are made to trypticase soy agar and Albimi agar plates on the fourth day and thereafter at regular intervals unless growth occurs All cultures should be incubated at 37° C in closed jars containing an atmosphere with 10 per cent carbon dioxide The initial cultures should be kept for at least one month unless growth appears earlier

Cultures of sternal marrow or of an enlarged cervical lymph node may be positive when the blood is negative These procedures may be particularly useful in long standing chronic cases

The agglutination test when properly done is an invaluable aid in diagnosis The reliability depends upon the use of a standardized antigen prepared from a completely smooth culture of any of the three species of *Brucella* After growth on solid media and suspension in saline solution the organisms should be killed by heat formaldehyde or phenol and the suspension standardized by turbidimetric methods and tested against sera of known titer The serial dilution test tube method should be used and the serum antigen mixture incubated at 37° C for 18 to 24 hours before reading

A titer of 1/320 or higher justifies a presumptive diagnosis of brucellosis and a lower initial titer followed by a rising titer may have considerable significance

Various other diagnostic procedures have been recommended The complement fixation test has no advantages over the agglutination reaction Dermal sensitivity tests have the same significance as the tuberculin test and consequently are of no assistance in diagnosis Their use is often followed by a high titer of agglutinins which may confuse the interpretation of the agglutination reaction The opsonocytophagic test is of little value and is not recommended The use of the Ouchterlony agar diffusion plates may be of some value in certain studies of *Brucella* Cultures of *Br melitensis* have been found to yield a diffusible precipitin antigen which produces lines with antisera of rabbits goats and cattle

that had been infected with either *Br abortus* or *Br melitensis* The lines of precipitation varied in number from one to three

A comparable antigen could not be prepared from *Br abortus* and *Br suis* cultures by the methods which were effective in producing an antigen from *Br melitensis* Further development of this technique may make it of value in the specific diagnosis of brucellosis

Treatment Aureomycin chloramphenicol (Chloromycetin) oxytetracycline (Terramycin) and dihydrostreptomycin have proved to be effective therapeutic agents for both acute and chronic brucellosis They have replaced all other forms of therapy

Combined treatment using Aureomycin or Terramycin and dihydrostreptomycin over a period of 12 to 14 days is the preferred treatment for the acute disease The recommended dosages for an adult are

Aureomycin or Terramycin 3 0 grams daily in divided dosage by mouth dihydrostreptomycin 1 0 gram twice daily intramuscularly

Aureomycin alone has given good results in the treatment of the acute stage and of relapses The dosage recommended by the FAO/WHO Expert Panel on Brucellosis is Aureomycin 2 to 4 grams daily for 14 to 21 days

Chloromycetin is active against all three strains of *Brucella* A total of 15 to 20 grams over a period of six to ten days is advised for adults This should be administered in accordance with the following schedule 50 to 100 mgm per kilogram daily in divided dosage every three to four hours until the patient is afebrile when the daily dose may be reduced to a total of 1 5 to 2 0 grams

Cases of chronic brucellosis may require more protracted treatment

Prophylaxis Since there is no satisfactory method for artificial immunization prevention depends upon avoidance of infection The widespread geographic distribution the occurrence of the *Brucella* in a variety of animals and the resistance of the organisms provide many op[illegible] in almost [illegible] d or drink [illegible] The most important factors in prophylaxis are a properly protected water supply and avoidance of unpasteurized milk and milk products

25

Tuberculosis

Emanuel Suter

Synonyms White plague phthisis consumption "Grosse Krankheit"

Definition. Tuberculosis is an infectious disease of man and animals caused by *Mycobacterium tuberculosis* (Zopf 1883) The disease is characterized by a chronic course and a great variability in the host s reaction to the presence of tubercle bacilli The infectious process may be limited to the portal of entry and the regional lymph nodes (most fre

or it may
destruc
xacerba

tions The tissue reaction to the presence of tubercle bacilli results in formation of typical tubercles from which the name of the disease is derived

Distribution. Infections with mycobacteria have world wide distribution The natural reservoirs of the agent of human tuberculosis are man and dairy animals Prevalence severity and clinical types of the disease are determined by socioeconomic hereditary and other factors Environmental conditions such as migrations of populations nutrition and wars may influence the course of the disease in the individual and also its epidemiologic pattern Distribution and prevalence can therefore change rapidly

Etiology Tuberculosis in man and other mammals is caused by *Mycobacterium tuberculosis* (Zopf 1883) *M bovis* (Bergey *et al* 1934) *M avium* (Chester 1901) and *M microti* (Reed 1957) (= *M tuberculosis* var *muris*) Human infections are frequently caused by the bovine type in countries with a high incidence of tuberculosis in cattle However in countries where this type has been eradicated infections in man are almost exclusively of the human variety A new type of mycobacteria has recently been isolated from cases of pulmonary tuberculosis in man in some areas of the United States The classification of these

pleomorphism depending on the strain and source of the culture (in vivo or in vitro) Their size is approximately 1 to 4 by 0.2 to 0.5 μ. The bacteria frequently appear beaded They are gram positive and retain

basic dyes when treated with acid This acid fastness is highly specific for mycobacteria and is shared by only a few other pathogenic organ isms *Actinomyces* and *Nocardia* Tubercle bacilli are strictly aerobic and form little or no acid on culture media They are capable of growth in simple media containing mineral salts glucose or glycerol as the carbon source with either amino acid preparations or protein hydrolysates as the source of nitrogen However the organisms are highly susceptible to the inhibitory action of certain contaminating compounds especially fatty acids and therefore their cultivation is greatly facilitated by the presence of some protein Growth is slow, the generation time being ap proximately 12 to 20 hours The individual organisms have a tendency to stick literally to each other resulting in a serpentine pattern of growth the so called cord formation The degree of cording has been used as a criterion for the determination of the virulence of a given strain Other characteristics of virulent strains are their capacity to retain neutral red in its acid form even under alkaline conditions and certain other bio chemical properties Another characteristic is their capacity to cause progressive tuberculosis in experimental animals such as guinea pigs mice hamsters rabbits and monkeys

Cultural Characteristics For the cultivation of mycobacteria dif ferent kinds of media are available and a choice depends on the purpose of cultivation Complex media are used for primary isolation for example the Loewenstein Jensen formula which has become standard in many countries and consists of mineral salts asparagin potato flour and whole egg It also contains 0 7 per cent glycerol a concentration which allows human and bovine strains to grow Usually a small concentration of malachite green is added (0 05 per cent) to prevent growth of con taminating microorganisms Depending on the number and physiologic state of the organisms growth is usually visible after two to four weeks The organisms form slightly yellowish dry raised granular colonies from which they cannot be finely dispersed unless triturated For large scale production of bacterial masses (production of tuberculin and BCG vaccine) surface cultures on liquid media in large bottles are used The media such as Sauton s or Lockemann s are semisynthetic and contain up to 5 per cent glycerol For experimental purposes Dubos liquid medium containing "Tween 80 (0 05 per cent) bovine serum albumin (0 5 per cent) mineral salts and a digest of casein is most suitable The organisms grow in the depth of the medium and are easily dispersible

Differentiation between the various species of *Mycobacterium tuber culosis M bovis M avium* and *M microtus* and the CAF strains is based on a number of criteria which are briefly summarized in Table IV 10 Differentiation can be of importance for epidemiologic informa tion and for the evaluation of individual cases Optimal growth of most strains is obtained at temperatures between 35° and 40° C Two excep tions are *Mycobacterium ulcerans* and *M balnei* which grow between 25° and 35° C It is important to note that animal pathogenicity of the CAF organisms is variable even when isolated from active pulmonary lesions of man This is in contrast to the classic mycobacteria which are usually pathogenic for one animal species or another when freshly iso

Table IV.10. Characteristics Useful for the Differentiation of Mycobacteria Isolated from Man

CRITERIA	SPECIES OF MYCOBACTERIUM			CAF
	tuberculosis	*bovis*	*avium*	
Growth				
Loewenstein	eugonic (r)	dysgonic	eugonic (s)	eugonic (s)
Rate of growth	slow	slow	more rapid	more rapid
1% glycerol	+	−	+	+
Pigment	−	−	−	+
Morphology	rods	rods	rods & granules	rods & granules
Cord formation	+	+		−
Production of nicotinic acid	much	little	little	?
Inhibition by				
streptomycin	+	+	−	−
isoniazid	+	+	−	−
Pathogenicity				
guinea pig	+	+	−	−
rabbit	−	+	+	−
hamster	+	+	−	+ or −
mouse	+	+	+	+ or −
monkey	+	+	−	+ or −

lated An exception to this rule are catalase negative, isoniazid resistant human tubercle bacilli, which are usually avirulent for experimental animals

Epidemiology. Tubercle bacilli are either inhaled with aerosols produced by coughing, ingested with food from infected animals (dairy products), or swallowed by licking contaminated objects or fingers The infection is therefore likely to spread within households school classes or other groups Tuberculosis is an endemic infection, since it is constantly present in a given population group once it has been introduced True epidemics are rarely seen and then only under special circumstances, such as introduction of the agent into a group previously free of tuberculosis or abrupt changes of living conditions in an already infected population A high degree of correlation frequently exists between incidence of infection, morbidity and mortality Incidence of infection is a function of exposure and is therefore dependent on the source of infective material—sputum positive cases which are not isolated and especially crowded living conditions Incidence is greatly influenced by public health measures such as early detection and isolation of cases Morbidity and mortality are determined essentially by susceptibility of the individual or entire populations, massiveness of infection effectiveness of treatment general dietary standards physical exertion and other factors Mortality and prevalence of infection have decreased in most countries during the last 50 to 100 years In many countries this steady decrease was interrupted by the two World Wars Relatively abrupt increases of mortality have taken place in the past as a consequence of

Table IV.11. Tuberculosis Mortality* in Different Countries

COUNTRY	YEAR		
	1930	1940	1953
Argentina	129	91	40
Australia	50	37	11
Canada	77	50	12
Ceylon	68	62	30
Chile	264	261	82
England Wales	87	67	20
Finland	254	212	45
France	158	140	37
Iceland	216	86	9
Japan	187	210	66
Mexico	69	57	31
Netherlands	75	44	9
Norway	149	81	16
Puerto Rico	263	260	47
Spain	123	113	40
Switzerland	125	78	23
Union of South Africa	47	35	15
United States	71	46	12

* Per 100 000 population

industrialization and increasing urbanization Some figures on mortality of tuberculosis are given in Table IV 11

Pathogenesis and Pathology. The pathogenesis of the tuberculous lesion cannot be discussed or understood without a consideration of the role played by the immune response especially the importance of the emergence of delayed hypersensitivity, also called tuberculin type or infection hypersensitivity

Primary Tuberculosis When tubercle bacilli gain access to the respiratory part of the lung of a normal individual, an acute inflammatory reaction may occur *Monocytic cells rapidly replace the polymorphonuclear leukocytes* The tubercle bacilli are readily phagocytosed but are able to multiply intracellularly as well as extracellularly Some cell destruction will occur at this time The cord factor, a trehalose dimycolate, may play an important part during this early phase of infection Accumulation of mononuclear elements follows with formation of epithelioid and Langhans' giant cells The wax fraction of the tubercle bacillus is considered to be responsible for this reaction, since these waxes alone are capable of eliciting a typical granulomatous response when injected into experimental animals This activity is not specific, however, but is shared by many other fatty acids not found in tubercle bacilli Eventually central caseous necrosis occurs in the granuloma at about the same time as the host becomes sensitive to tuberculin For this reason it is assumed that delayed hypersensitivity at least contributes to caseation necrosis

Under favorable conditions for the host, the process is arrested with encapsulation of the lesion by lymphocytic elements and fibroblasts

Under less favorable conditions the tubercle will grow centrifugally and involve adjacent tissue The progressing lesion may involve lymphatics bronchi and blood vessels Lymphatic spread with lymphadenitis canalicular spread with dissemination throughout the lungs and involvement of vessels may lead to dissemination of organisms to distant organs with resulting miliary tuberculosis or localization in single organs The primary lesion is limited to the first lodgement of the bacilli in the tissues and the regional lymph nodes Most frequently this occurs in the lungs involving a subpleural area of the upper lobe and the regional lymph node This is called the Ghon complex The primary complex can also be located in the tonsils and the cervical lymph nodes or in the small intestine including the mesenteric lymph nodes

Postprimary Tuberculosis Reinfection either endogenous as described above or exogenous can occur at any time after the primary infection The reaction to this new deposition of tubercle bacilli is more intense and rapid and can lead to extensive caseation (caseous pneumonia) if the host is highly hypersensitive Provided the number of reinfecting bacilli is small the tissues are more resistant to the secondary invasion resulting in a more restricted lesion with less likelihood of further spread Two groups of postprimary tuberculosis have been distinguished One group secondary tuberculosis includes the more acute diseases with preponderance of allergic manifestations The other group tertiary tuberculosis is classified by chronic and productive processes Secondary tuberculosis encompasses tuberculous meningitis miliary tuberculosis exudative pleurisy and tuberculous peritonitis Phthisis tuberculosis of the genitourinary tract and the bones and lupus vulgaris are the major diseases belonging to the group of tertiary tuberculosis

Clinical Characteristics The clinical picture of tuberculosis depends on the type and localization of the process and the severity of involvement Therefore the symptoms of the disease are as varied as its localization and severity General symptoms are weakness weight loss elevated body temperature night sweats alterations of peripheral leukocyte counts and an elevated sedimentation rate Specific symptoms correspond to the organ involved and their severity is often but not always related to the degree of destruction caused by the infectious process Remissions and relapses are frequently observed especially in pulmonary tuberculosis Some forms of tuberculosis are benign others are progressive and fatal

Diagnosis Clinical manifestations x ray findings and a history of previous exposure usually allow a tentative diagnosis of tuberculosis However information obtained by these means can be misleading and additional more specific diagnostic aids are necessary The most important of these are the tuberculin skin test demonstration and isolation of the etiologic agent (p 176) and serologic tests

The most reliable technique for tuberculin testing is the intradermal injection of "Old Tuberculin" or its purified product PPD (purified protein derivative) the so called Mantoux test In infected man or animals a typical delayed skin reaction will appear within 24 hours The reaction begins as an area of redness and induration and is frequently

followed by central necrosis The reaction persists for at least 48 to 72 hours and much longer if necrosis occurs The reaction should be read 48 to 72 hours after injection of the antigenic material The skin re sponse in the normal individual is negligible However, cross reactions are possible, especially in people infected with *Histoplasma capsulatum* The interpretation of the skin test is as follows

Positive Reaction Current, active infection
Old arrested infection
Previous vaccination with BCG
If weak a nonspecific reaction

Negative Reaction No infection
Very recent infection in the preallergic phase
Infection but individual does not react
Arrested infection with conversion to negativity
Terminal anergic phase
Infection with CAF

In addition to being a valuable aid for diagnosis tuberculin testing is highly useful for epidemiologic surveys, supervision of individuals who are frequently exposed and environmental investigation of newly de tected cases

The demonstration and isolation of *Mycobacterium tuberculosis* or chromogenic acid fast organisms provides conclusive evidence of tuber culous infection The specimens to be investigated depend on the local ization of the disease Although the demonstration of acid fast organisms in a smear is frequently sufficient the presence of saprophytic organisms can never be excluded by this means Therefore the isolation of the organism is highly desirable and necessary if drug sensitivity should be determined

Among serologic tests the Middlebrook Dubos hemagglutination test is the test of choice For this test sheep or human type O red blood cells are sensitized with old tuberculin and added to serial twofold dilutions of the patient s serum In the presence of antibodies the red cells will be agglutinated However the diagnostic significance of this test has not yet been evaluated The major difficulty is that false positive reactions are possible

Treatment Until very recently the best treatment of tuberculosis was possible only in sanatoria or hospitals Owing to the effectiveness of chemotherapy treatment for certain selected types of tuberculosis now can be performed in the home This should be of great help in countries where no or very limited sanatorium facilities exist and where tuber … son 17 d and
culos … m
PAS … or
binat …
delay the establishment of organisms resistant to either chemotherapeutic agent Therapy with these agents has been highly successful has short ened the period of illness and has made previously incurable forms of tuberculosis curable This is especially true for tuberculous meningitis

and miliary tuberculosis Therapeutic success depends on the form and the stage of the disease

The greatest difficulties during treatment arise from drug toxicity and the emergence of drug resistant organisms since the disease requires prolonged administration of the drugs Tubercle bacilli resistant to isoniazid are found in about 60 per cent of the cases treated with this agent If the resistance to isoniazid is high the organisms frequently are no longer pathogenic for experimental animals However it has not been fully established whether these organisms are still of pathogenic importance within the lesion from which they were isolated

Prophylaxis *Prevention of Infection* Detection and isolation of active and sputum positive cases has been most effective Under certain circumstances the removal of children from tuberculous parents is desirable but this procedure does not eliminate the danger of contaminating other people The hazards of infection can be reduced greatly by instructing the patient how to avoid excessive spread of tubercle bacilli

Active Immunization Immunization with BCG an attenuated strain of bovine tubercle bacilli is practiced in many countries Since the end of World War II millions of children have been vaccinated and their subsequent course followed by the World Health Organization BCG vaccine usually is injected intradermally or may be applied by multiple puncture There is substantial evidence that this procedure provides a certain degree of protection as manifested by decrease of morbidity and mortality in vaccinated groups compared with control groups About 95 per cent of vaccinated individuals become tuberculin positive within three to six weeks In a certain percentage of people there is a self limited ulcerating lymphadenitis Only a few well documented cases have been reported in which BCG caused a progressive fatal infection In all of these the tissue reaction to the tubercle bacilli was unusual and those isolated were typically attenuated BCG organisms The benefits of BCG vaccination especially in countries with low mortality rates for tuberculosis have been the subject of much discussion A committee appointed by the Surgeon General of the United States Public Health Service has made some recommendations for BCG vaccination

1. Vaccination should be general in countries with high mortality from tuberculosis
2. Vaccination is advisable for limited population groups in countries with low mortality from tuberculosis including
   a. Physicians nurses medical and nursing students laboratory workers and hospital employees
   b. Persons unavoidably exposed to continued contact with infectious cases of tuberculosis in the home
   c. Patients inmates and employees of institutions such as mental hospitals and prisons in which exposure is likely to be high

It has been suggested recently that the vaccine be given by the respiratory route Excellent results have been obtained by this technique in mice and it remains to be seen whether it can be applied usefully in man In countries where for cultural reasons people resist any kind of injections this form of application of the vaccine might prove to be very helpful

followed by central necrosis The reaction persists for at least 48 to 72 hours and much longer if necrosis occurs The reaction should be read 48 to 72 hours after injection of the antigenic material The skin response in the normal individual is negligible However, cross reactions are possible, especially in people infected with *Histoplasma capsulatum* The interpretation of the skin test is as follows

Positive Reaction	Current, active infection
	Old arrested infection
	Previous vaccination with BCG
	If weak, a nonspecific reaction
Negative Reaction	No infection
	Very recent infection in the preallergic phase
	Infection, but individual does not react
	Arrested infection with conversion to negativity
	Terminal anergic phase
	Infection with CAF

In addition to being a valuable aid for diagnosis, tuberculin testing is highly useful for epidemiologic surveys, supervision of individuals who are frequently exposed, and environmental investigation of newly detected cases

The demonstration and isolation of *Mycobacterium tuberculosis* or chromogenic acid fast organisms provides conclusive evidence of tuberculous infection The specimens to be investigated depend on the localization of the disease Although the demonstration of acid fast organisms in a smear is frequently sufficient, the presence of saprophytic organisms can never be excluded by this means Therefore, the isolation of the organism is highly desirable and necessary if drug sensitivity should be determined

Among serologic tests the Middlebrook-Dubos hemagglutination test is the test of choice For this test, sheep or human type O red blood cells are sensitized with old tuberculin and added to serial twofold dilutions of the patient's serum In the presence of antibodies the red cells will be agglutinated However, the diagnostic significance of this test has not yet been evaluated The major difficulty is that false positive reactions are possible

Treatment. Until very recently the best treatment of tuberculosis was possible only in sanatoria or hospitals Owing to the effectiveness of chemotherapy, treatment for certain selected types of tuberculosis now can be performed in the home This should be of great help in countries where no or very limited sanatorium facilities exist and where tuberculosis until recently was not treated at all Streptomycin, isoniazid and PAS (para aminosalicylic acid) are the drugs of choice *Usually a combination* of streptomycin with isoniazid or PAS is used to prevent or delay the establishment of organisms resistant to either chemotherapeutic agent Therapy with these agents has been highly successful has shortened the period of illness and has made previously *incurable forms* of tuberculosis curable This is especially true for tuberculous meningitis

and miliary tuberculosis Therapeutic success depends on the form and the stage of the disease

The greatest difficulties during treatment arise from drug toxicity and the emergence of drug resistant organisms, since the disease requires prolonged administration of the drugs Tubercle bacilli resistant to isoniazid are found in about 60 per cent of the cases treated with this agent If the resistance to isoniazid is high, the organisms frequently are no longer pathogenic for experimental animals However, it has not been fully established whether these organisms are still of pathogenic importance within the lesion from which they were isolated

Prophylaxis. *Prevention of Infection* Detection and isolation of active and sputum positive cases has been most effective Under certain circumstances the removal of children from tuberculous parents is desirable, but this procedure does not eliminate the danger of contaminating other people The hazards of infection can be reduced greatly by instructing the patient how to avoid excessive spread of tubercle bacilli

Active Immunization Immunization with BCG, an attenuated strain of bovine tubercle bacilli is practiced in many countries Since the end of World War II millions of children have been vaccinated and their subsequent course followed by the World Health Organization BCG vaccine usually is injected intradermally or may be applied by multiple puncture There is substantial evidence that this procedure provides a certain degree of protection, as manifested by decrease of morbidity and mortality in vaccinated groups compared with control groups About 95 per cent of vaccinated individuals become tuberculin positive within three to six weeks In a certain percentage of people there is a self limited ulcerating lymphadenitis Only a few well documented cases have been reported in which BCG caused a progressive fatal infection In all of these, the tissue reaction to the tubercle bacilli was unusual and those isolated were typically attenuated BCG organisms The benefits of BCG vaccination, especially in countries with low mortality rates for tuberculosis, have been the subject of much discussion A committee appointed by the Surgeon General of the United States Public Health Service has made some recommendations for BCG vaccination

1 Vaccination should be general in countries with high mortality from tuberculosis
2 Vaccination is advisable for limited population groups in countries with low mortality from tuberculosis, including
   a Physicians nurses, medical and nursing students laboratory workers and hospital employees
   b Persons unavoidably exposed to continued contact with infectious cases of tuberculosis in the home
   c Patients inmates and employees of institutions, such as mental hospitals and prisons in which exposure is likely to be high

It has been suggested recently that the vaccine be given by the respiratory route Excellent results have been obtained by this technique in mice, and it remains to be seen whether it can be applied usefully in man In countries where, for cultural reasons, people resist any kind of injections, this form of application of the vaccine might prove to be very helpful

Eradication Bovine tuberculosis can theoretically and practically be eradicated but this is usually not attempted because the economic consequences are too great The United States has been highly successful in this respect Pasteurization of milk is helpful but it does not prevent contamination from other dairy products

Chemoprophylaxis This mode of prophylaxis is still in dispute It has been suggested to treat both people with known exposure and those who have converted recently to tuberculin positivity with isoniazid over a period of several months either to prevent infection or to forestall the evolution of primary infections into the secondary phase However the benefits of such treatment are not yet established and the problem requires further investigation Furthermore it might prove very difficult to treat healthy people over a long period

26

Leprosy

H W Wade

Synonyms *Lepra la lepre Aussatz spedalskhed* Hansens disease

Definition Leprosy is an infectious disease of low contagiosity and chronic course caused by *Mycobacterium leprae* and generally characterized by conspicuous skin and nerve lesions and their sequelae The disease has an incubation period which usually cannot be determined but typically is prolonged Abundant variations of the disease produce several clinical forms or varieties which fall into two general groups the *malign* (or *lepromatous*) and the *benign* (or *nonlepromatous* comprising several varieties) Nonlepromatous cases exhibit resistance to the infection evidenced by paucity of bacilli in the lesions and their tissue reactive structure in the lepromatous type there is obvious lack of resistance with an abundance of bacilli in the lesions

Distribution The disease is widely distributed in tropical and subtropical regions It occurs throughout most of Asia with a high prevalence in India and other countries of southeast Asia southern China and in some of the Pacific islands It is particularly widespread in central Africa and has become endemic in much of the Western Hemisphere especially in certain South and Central American countries The disease occurs widely in Mexico In the continental United States leprosy is indigenous but on a low level in southern California Florida (chiefly

in Key West and Tampa) Louisiana and southeastern Texas There are probably more than five million cases in the world

Etiology *Mycobacterium leprae* is an acid fast gram positive non sporeforming nonmotile pleomorphic bacillus The slender rod shaped bacteria often stain unevenly or irregularly with a resultant beaded appearance It has certain morphologic resemblances to *M tuberculosis* but shows less affinity for an acid fast stain Studies by electron microscopy of the bacillus in smears and sections of lesions have not as yet revealed any particularly distinctive feature perhaps because there is no way of obtaining preparations that contain only young and viable organisms The leprosy bacillus has not been cultivated successfully and until very recently attempts to produce leproma like lesions in experimental animals have failed completely In the patient s lesions the bacilli are mostly intracellular they multiply abundantly in the cells of the lepromatous lesions In the "lepra cell" or "Virchow cell the mass or group of bacilli may lie in a matrix or *gloea* the combination comprising the *globus*

Epidemiology The communicability of leprosy is low Infection seems to depend mainly upon prolonged and intimate contact with persons with infectious forms of the disease Susceptibility varies greatly among different individuals and probably to some extent among different races it is much higher in childhood than in adult life Among adults the disease is often twice as common in men as in women except among Africans in whom the sex difference is usually slight Although the conditions necessary for transmission cannot be defined the skin and to some extent the nasal mucous membranes are believed to be the usual portals of entry There is no definite incubation period Ordinarily several years elapse before manifestations appear and the latent period may be as long as 30 years

Pathology The principal skin lesions of leprosy vary from the simplest macule to thick patches of the major tuberculoid variety or the furrowed infiltrations of advanced lepromatous cases No leprosy lesions are of "id" character All are due to the presence of the bacilli although in lesions of the benign forms these are usually so sparse that they are not demonstrable by the standard smear technique The peripheral nerve trunks are involved in both benign and malign forms although ordinarily by different routes and this involvement is one of the most important elements of the disease

In lepromatous leprosy the superficial lymph nodes the upper respiratory tract and the eyes are often conspicuously involved The spleen liver and testes are also affected but only in the last is there disturbance of function Bacilli may sometimes be demonstrable in the blood during the severe reactions (lepra fever) Involvement of the peripheral nerve trunks is important in all forms of the disease

Histologically the infiltrates in the skin of whatever type affect primarily the zones of vascular areolar tissue Involvement of dermal nerve branches is unique among cutaneous infections and virtually constant Lesions in other structures including those in the nerve trunks



Figure IV 9 A marked lepromatous infiltration, showing flattening of the epidermis with hyperkeratosis and the characteristic free zone below The infiltrate is a solid mass of lepra cells with many small globus spaces Note beginning of change to the foamy condition.

(except when caseation occurs in tuberculoid nerve lesions) correspond to the different types occurring in the skin

The only distinctive lesion of leprosy is the *leproma* This is a granuloma composed mainly of massed macrophages altered to form the lepra cells of Virchow lying in a well vascularized supporting stroma (Fig IV 9) These cells harbor but do not destroy the bacilli and in the classic lesion they become vacuolated by the formation of globi (Fig IV 10 top and center) "Giant globi are often found within foreign body giant cells or ensheathed in a sort of syncytium and at times they constitute veritable microcolonies However some lepromas may be composed of massed spindle shaped cells loaded with bacilli in which globus formation is absent As the lesions gradually age the lepra cells become foamy multivacuolated and often multinucleated They then contain few bacilli but much acid fast lipid c material

As the infiltrate in the skin increases it disrupts the normal architecture and seriously affects the accessory structures These persist however even in massive lesions except in the tumor like secondary nodules which are pure lepromas The subcutis is commonly invaded and subcutaneous nodules may develop

The lepromatous infiltrate in the peripheral nerve trunks involves the endoneurium but despite its intensity functional disturbance is long delayed unless reactional inflammation supervenes

The tissue reactive *tuberculoid* lesions are nonspecific in character, presenting focal masses of epithelioid cells with variable degrees of lymphoid cell accumulation and giant cell formation (Fig IV 11) The epithelioid cells ingest and destroy the bacilli When bacilli are demonstrable, they are usually in other cells or other structures, especially the nerves The more marked lesions of the skin resemble noncaseating tuberculosis or Boeck's sarcoid, except for the involvement of the nerve branches Extension of the process may be seen in the nerves of the subcutis, and caseation necrosis occasionally occurs

In the lesser degrees of clinically tuberculoid lesions the epithelioid foci tend to be correspondingly smaller and more isolated In their simplest form they appear as "pretuberculoid" groups of a few epithelioid cells which are often found in clinically simple flat macules In reactional tuberculoid conditions the lesions are massive and less orderly When such cases evolve to the borderline stage, the picture is even more atypical and confused At times both tuberculoid and lepromatous changes may coexist, a condition sometimes called 'dimorphous'

Simple chronic inflammatory round cell infiltration is found in many pale, flat [illegible]
leprosy" [illegible]
type may [illegible]
[illegible]

[illegible] rosy cases is based on clinical and bacteriologic features primarily, aided by immunologic and histopathologic criteria This important subject is one of interminable discussion and dispute However in the spectrum of forms and varieties there is general recognition of two types lepromatous (malign) and tuberculoid (benign) so far apart and dissimilar that they are often called "polar" The lepromin test usually is positive in

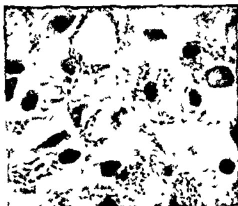


Figure IV 10 Lepra cells in a skin lesion of lepromatous leprosy Large mononuclear phagocytes loaded with *M leprae* some exhibiting different degrees of vacuolation due to globus formation from the spaces of which most bacilli have escaped during preparation.



Figure IV.11. Tuberculoid lesions of leprosy A. Multiple epithelioid foci in one place in contact with the epidermis in a clinically minor tuberculoid lesion of moderate degree (80 X) B. A sarcoid like focus showing massed epithelioid cells and a Langhans giant cell with lymphoid cell accumulation on one side (150 X) (Courtesy of Dr H. W Wade)

patients with the tuberculoid type of leprosy, whereas the reaction ordinarily is negative in the lepromatous type There is also wide acceptance of two lesser forms, indeterminate and borderline The indeterminate form is an early, macular, benign stage of the disease which, if not interrupted, may evolve into one of the polar types, the lepromin reaction may be positive or negative The borderline form is a lepromin negative malign form which results from an unfavorable development in tuberculoid cases, the position of these cases in the spectrum is toward the lepromatous, and they can become definitely lepromatous There are numerous advocates for recognition of two other forms, pure neural (or neuritic) and maculoanesthetic, but the terms do not yet have international acceptance

General The onset of leprosy is usually insidious There are no definite prodromata, although some patients may complain of early sensory disturbances or neuritic pain Occasionally the disease appears abruptly in a spectacular reactional form

Early leprosy is often difficult to recognize Typically, there are one or a few small, well defined, simple, indeterminate macules These are anesthetic and hypopigmented Some cases, apparently lepromatous from the outset, present diffusely outlined, erythematous macules with little, if any, perceptible infiltration, no marginal thickening or differentiation between margin and center, little or no anesthesia, but positive bacteriologic findings These lesions may be found on the extremities, on the body, more commonly on the back than anteriorly, often on the buttocks and not infrequently on the face (Fig IV 12) In advanced cases

whatever the form there are naturally immune areas the cubital and popliteal fossae the axillary and inguinal regions the retroauricular area and generally the scalp

The evolution of the indeterminate cases is variable Some clear up spontaneously others persist and progress indefinitely as "maculoanesthetic in still others increase of tissue reactivity leads to the development of the tuberculoid form or conversely loss of resistance results in transformation into the lepromatous type Tuberculoid cases may persist as such for long periods There may be wide extension of the lesions but ultimately they tend to subside spontaneously On the other hand they may change to the borderline type and from that they occasionally *become frankly lepromatous Lepromatous cases seldom change in type* and are usually progressive if not effectively treated

The color of the lesions may vary considerably apart from the influence of racial characteristics In the macular lesions there is dissociation of sensation Discrimination between heat and cold is lost first then sensitivity to pain and finally tactile sense Perception of pressure remains intact In most lesions there is little or no sweating and hairs are usually absent Atrophy of the skin may occur in resolved lesions or parts of lesions on the other hand the texture and even the color may return to normal Ichthyosis of the legs is common and there may be marked thickening of the skin of the lower extremities in advanced lepromatous cases

Frequently there is thickening and often tenderness of the peripheral nerve trunks at the points of flexure the ulnars above the elbows the external peroneals at the knees and also the great auriculars These are important diagnostic signs

Degeneration of the trunk nerves leads to anesthetic paralytic and trophic changes of the extremities followed by mutilations often aggravated by trauma Muscle atrophy of the hands becomes conspicuous contractures slowly develop and the bones of the phalanges gradually undergo absorption or become necrotic infected and extruded (Fig IV 13) The soft tissues of the fingers are absorbed leaving distorted

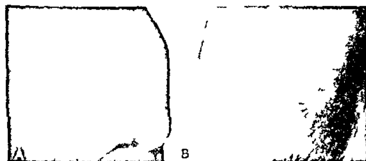


Figure IV 12 Macular lesions of leprosy A. Simple (indeterminate) macule on the buttock active progression indicated by the streaming outline B Minor tuberculoid lesion of the arm, superficial, with micropapulate elevated marginal zone of activity and healed center (Courtesy of Dr H W Wade)



Figure IV.11. Tuberculoid lesions of leprosy A. Multiple epithelioid foci in one place in contact with the epidermis in a clinically minor tuberculoid lesion of moderate degree (80 X) B. A sarcoid like focus showing massed epithelioid cells and a Langhans giant cell, with lymphoid cell accumulation on one side (150 X) (Courtesy of Dr H W Wade)

patients with the tuberculoid type of leprosy, whereas the reaction ordinarily is negative in the lepromatous type There is also wide acceptance of two lesser forms, indeterminate and borderline The indeterminate form is an early, macular, benign stage of the disease which, if not interrupted, may evolve into one of the polar types, the lepromin reaction may be positive or negative The borderline form is a lepromin negative malign form which results from an unfavorable development in tuberculoid cases, the position of these cases in the spectrum is toward the lepromatous, and they can become definitely lepromatous There are numerous advocates for recognition of two other forms, pure neural (or neuritic) and maculoanesthetic, but the terms do not yet have international acceptance

General The onset of leprosy is usually insidious There are no definite prodromata, although some patients may complain of early sensory disturbances or neuritic pain Occasionally the disease appears abruptly in a spectacular reactional form

Early leprosy is often difficult to recognize Typically, there are one or a few small, well defined, simple, indeterminate macules These are anesthetic and hypopigmented Some cases, apparently lepromatous from the outset, present diffusely outlined, erythematous macules with little, if any, perceptible infiltration, no marginal thickening or differentiation between margin and center, little or no anesthesia, but positive bacteriologic findings These lesions may be found on the extremities, on the body, more commonly on the back than anteriorly, often on the buttocks, and not infrequently on the face (Fig IV.12) In advanced cases

whatever the form, there are naturally immune areas the cubital and popliteal fossae, the axillary and inguinal regions, the retroauricular area, and generally the scalp

The evolution of the indeterminate cases is variable Some clear up spontaneously, others persist and progress indefinitely as "maculoanesthetic," in still others, increase of tissue reactivity leads to the development of the tuberculoid form, or conversely, loss of resistance results in transformation into the lepromatous type Tuberculoid cases may persist as such for long periods There may be wide extension of the lesions but ultimately they tend to subside spontaneously On the other hand they may change to the borderline type, and from that they occasionally become frankly lepromatous Lepromatous cases seldom change in type and are usually progressive if not effectively treated

The color of the lesions may vary considerably, apart from the influence of racial characteristics In the macular lesions there is dissociation of sensation Discrimination between heat and cold is lost first, then sensitivity to pain and finally tactile sense Perception of pressure remains intact In most lesions there is little or no sweating and hairs are usually absent Atrophy of the skin may occur in resolved lesions or parts of lesions, on the other hand the texture and even the color may return to normal Ichthyosis of the legs is common, and there may be marked thickening of the skin of the lower extremities in advanced lepromatous cases

Frequently there is thickening and often tenderness of the peripheral nerve trunks at the points of flexure, the ulnars above the elbows, the external peroneals at the knees, and also the great auriculars These are important diagnostic signs

Degeneration of the trunk nerves leads to anesthetic paralytic and trophic changes of the extremities, followed by mutilations often aggravated by trauma Muscle atrophy of the hands becomes conspicuous, contractures slowly develop, and the bones of the phalanges gradually undergo absorption, or become necrotic infected and extruded (Fig IV 13) The soft tissues of the fingers are absorbed, leaving distorted

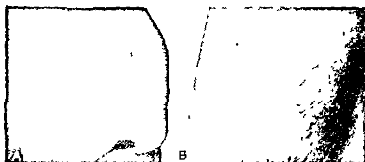


Figure IV 12 Macular lesions of leprosy A Simple ("indeterminate") macule on the buttock active progression indicated by the streaming outline B Minor tuberculoid lesion of the arm, superficial, with micropapulate elevated marginal zone of activity and healed center (Courtesy of Dr H W Wade)



Figure IV 13 Advanced trophic changes of the hands due to severe nerve damage with muscular atrophy contractures and progressive absorption of the digits on some of which residua of the nails can be seen.

residua of the nails on the stumps of the hands Wristdrop is occasionally seen Similar changes occur in the feet, and troublesome trophic ulcers develop on the plantar surfaces There are seemingly "pure neural" or "polyneuritic" cases which present only such changes

In its ordinary course leprosy is a nontoxic disease despite the immense numbers of bacilli in the lepromatous lesions The ultimate deterioration of such cases, producing indolent bacillus discharging ulcerations and other changes, comes on very gradually However, acute episodes of "lepra reaction," with or without fever, apparently allergic in nature, occur in many cases These reactions, which differ greatly in the different types, may be harmful

Death from leprosy itself is infrequent Pulmonary tuberculosis and nephritis are common terminal events, although the frequency of tuberculosis has greatly diminished since the advent of sulfone treatment Amyloidosis is often found at autopsy

Lepromatous Leprosy Symmetric distribution of the lesions is typical The brownish red lepromatous macules or infiltrations often appear first on the face but may be on other parts of the body Thickening of the earlobes is sometimes an early development As the disease progresses, the lesions increase in numbers, size and thickness, the infiltrations appearing smooth and tense and discrete nodulations or the leonine furrowing of the face may appear (Fig IV 14) The loss of eyebrows is often significant in type diagnosis

In advanced cases, ulceration of the nasal mucosa may lead to perforation of the cartilaginous septum and to falling of the nose Infiltration of the vocal cords causes the characteristic raucous voice, and occasionally leads to severe stenosis The eyes may be involved either by extension of infiltration from the conjunctiva to the cornea or by involvement of the uveal tract

Mild lepra reactions in this type of the disease are often beneficial, leading to recession of the lesions If they are severe and repeated, however, they are harmful, ulcerations of the skin may occur, especially on the extremities, and also acute neuritis, iridocyclitis or orchitis Also in this type, usually in cases improving under treatment, an erythema nodosum like reaction occurs,
which typically are tender,
and usually of short durati
chronic, producing dense indurations on the extremities It is questionable if this condition is beneficial

The peripheral nerve trunks are usually much more thickened than in "neural" cases because of the amount of specific lepra cell infiltration When nerve damage finally occurs the resulting sequelae produce the



Figure IV 14 An advanced lepromatous case with leonine face both furrowed and nodulate and with marked involvement of the forearms and hands less of the upper arms and still less of the body





Figure IV 15 Figure IV 16 Figure IV 17

Figure IV 15 Major tuberculoid plaque of face of reactional origin, in a Chinese patient. Isolated nodules on chin and other cheek are of the same nature reactional dissemination. (The grossly thickened right great auricular nerve in relation to the plaque is not demonstrated) (Courtesy of Dr H. W Wade)

Figure IV 16 Multiple broad margined tuberculoid macules of back spreading and fusing in a South African patient. Note central healing with recovery of normal color and texture in the largest one (Courtesy of Dr H. W Wade)

Figure IV 17. A borderline case in febrile reaction (an Indian patient) Modified tuberculoid lesions on chest and shoulder abruptly outlined plaques on face Ear has lepromatous aspect. (Courtesy of Dr H. W Wade)

picture of "complete leprosy" (Leloir), a stage often but unfortunately called "mixed" leprosy

Maculoanesthetic Leprosy This benign group comprises many of the cases having simple macules and in the older sense, many of those of the lesser tuberculoid type In these cases the skin lesions persist increase in numbers and spread centrifugally, at times with fusion of adjacent lesions

If the process is not arrested involvement of peripheral nerves becomes evident sooner or later Typically, there is less thickening of the nerve trunks than occurs in lepromatous leprosy In some instances attacks of acute neuritis hasten and intensify the nerve damage In many cases the skin lesions will disappear spontaneously, and neural manifestations if present, may be so slight that the recovered patients appear practically normal Often however, they are crippled and deformed (Fig IV 13)

Paralysis of the lower eyelids results in lagophthalmos and traumatic corneal damage is apt to follow There may be paralysis of the orbicularis oris muscles and even of the masseters Occasionally, nasal ulcers develop in which case the bacilli can be demonstrated in this lesion but not elsewhere

Tuberculoid Leprosy This variety of the benign form is characterized primarily by distinctive skin lesions presenting more or less elevation In spite of this they are still called macules (Figs IV 15 IV 16) In the common minor variety the elevation, which usually has an irregular

or micropapulate surface, occurs only in the outer advancing margin of the lesion or in a part of it In the less common major form there is more marked thickening and elevation of the marginal zone, which is broader, and the process tends to show deeper extension Recent lesions of this sort may show incomplete central resolution, and those of reactional origin may be solid plaques Hyperesthesia is often found in the active outer zones of the tuberculoid macules, and anesthesia in the central areas

Thickening of the cutaneous nerve cephalad to a lesion, especially of the major variety, is sometimes found It may extend to and involve, the corresponding nerve trunk This condition is typically asymmetric and unilateral, which is distinctive Massive thickening, especially if it is irregular, signifies caseation necrosis which may undergo liquefaction to produce a nerve abscess

The reactional lesions of the skin in this type are often spectacular They may easily be mistaken for lepromatous lesions, especially when there are disseminated metastatic nodules With repeated severe reactions, change to the atypical borderline form of the disease is liable to occur

Borderline Cases These cases belong to the malign group and may progress to become truly lepromatous In the past they have usually been classed as lepromatous, sometimes called atypical because of the asymmetry of the lesions and other peculiarities (Fig IV 17) However, if not too far advanced, they may regress to the original tuberculoid form In general they respond better to treatment than do real lepromatous cases

Diagnosis. *Bacteriologic Diagnosis* The cardinal diagnostic signs are the presence of anesthetic macular lesions or thickening and tenderness of peripheral nerve trunks and the demonstration of bacilli Search should be made for suspicious macules or infiltrations of the skin and for thickening of the earlobes and the eyebrows The peripheral nerves should be palpated carefully

Smears for bacilli should be made from several sites skin lesions earlobes and the nasal septum Since bacilli are usually obtainable only from lepromatous lesions many cases must be diagnosed on the basis of clinical appearance and the presence of anesthesia in simple macular or tuberculoid lesions In such lesions, loss of sensitivity to light touch and absence of pain on pinprick justify the diagnosis Tests for histamine flare and for sweating afford confirmatory evidence In the absence of skin lesions, muscular weakness of the face or areas of numbness on the extremities should be regarded as suspicious Polyneuritic anesthesias, stocking and glove distribution, will almost certainly be due to leprosy, especially if the nerve trunks are thickened.

The histamine flare test is performed by making a needle puncture into the skin through a drop of 1/1000 histamine acid phosphate solution The test is positive if there is no erythema flare when the puncture is made within the lesion area, or if the flare stops at the margin of the lesion when the puncture is made a little to the outside of it The sweating tests are seldom used



Figure IV 18 *Mycobacterium leprae* in stained smear from the nasal septum of an advanced lepromatous case with typical grouping but without globi or lepra cells

Smears for bacteriologic examination from the skin should be obtained by the scraped incision method which can be performed at any point in the lepromas and at the active marginal zone of leprids A fold of skin is compressed between thumb and forefinger, an incision is made well into the corium, and material is scraped from the cut surface with as little blood as possible Smears from the nasal mucosa should be made under direct observation using a speculum, searching the septum for infiltrations or ulcers In lepromatous cases bacilli may be very numerous (Fig IV 18) Puncture and aspiration of an enlarged lymph node or thickened ulnar nerve is rarely called for

Immunology There is no diagnostic test for leprosy, serologic or other, and what is known of its immunology derives largely from studies of the lepromin (Mitsuda) test The antigen of this test is a heat killed suspension of bacillus rich lepromas, intradermal injection into a fully reactive person elicits (1) the early (48 hour) Fernandez reaction and (2) the late (three week) Mitsuda reaction The former is an allergy reaction analogous to the tuberculin reaction but too inconstant even among contacts to be of diagnostic value The latter is a papulonodular lesion which appears in most nonlepromatous cases and also in many normal persons Lepromatous cases are, almost by definition nonreactive to lepromin The positive Mitsuda reaction demonstrates the presence of a reactivity which is regarded as signifying a degree of resistance to the disease This host resistance may prevent infection or determine the course of the disease The test has significance with respect to classification (see page 185) and prognosis

The abnormal proteins which develop in leprosy may cause false positive reactions in laboratory tests which depend upon protein frac-

tions, such as the cephalin flocculation test Serologic tests, for example, those for syphilis, may also be positive in this disease

Differential Diagnosis The lesions of leprosy are protean in character and resemble those of many other conditions Simple macular leprids must be distinguished from such conditions as tinea versicolor leukoderma (vitiligo), hypochromia of yaws, pale birthmarks and scars and certain lichenoid lesions In these conditions anesthesia is absent and the histamine and sweating tests are negative Syringomyelia, Raynaud's disease, Bernhardt's syndrome and other peripheral neuritic conditions may be confused with neural (polyneuritic) leprosy without skin lesions

Various lesions of tuberculoid leprosy, which is often misdiagnosed, must be distinguished from Boeck's sarcoid, granuloma annulare, lupus vulgaris, lupus erythematosus, tinea circinata, psoriasis and certain lesions of secondary syphilis and yaws With respect to the first two, the confusion may even extend to the histologic findings

[illegible] have to be dis
[illegible] sis mycosis fun
[illegible] of such lepromas
[illegible] d from the reac
tional lesions of the erythema nodosum type, they should be demonstrable elsewhere in the patient's skin

Treatment. General treatment, including personal and environmental hygiene, an ample well balanced diet and the correction of concomitant conditions is important With such measures even severe lepromatous cases often show some degree of amelioration at least for a time

Introduction of the sulfones revolutionized the treatment of leprosy and also opened new possibilities for the control of the disease by mass treatment Chaulmoogra preparations are virtually in disuse In advanced lepromatous cases sulfones are conspicuously useful in the rapid healing of skin ulcers and lesions of the upper respiratory tract, tracheotomies are now rare Early lepromatous cases clear up relatively rapidly as a rule If the skin lesions are well established, however, they recede slowly and the reduction of the bacterial index is still slower As a result, even responsive cases may require three or more years before smears become negative Improvement often seems to be slower at first in the non lepromatous forms of the disease The sulfones do not alleviate the effects of nerve damage, in fact, neural sequelae often develop in sulfone treated patients as skin lesions subside

Because of the toxicity of the parent substance 4 4'-diaminodiphenyl sulfone (DDS), relatively expensive derivatives (Promin, Diasone, Sulphetrone) were used exclusively at first When it was found that the much cheaper DDS could be used satisfactorily in proper dosage, the new treatment became much more generally available, including extensive use on an outpatient basis The derivatives still have their uses especially for certain cases which do not do so well on the parent substance

Dosage schedules of DDS vary considerably, by physicians' choice or depending on the tolerance of the individual patient, but the maximal

dose for inpatients is generally 100 mgm daily six times a week by mouth Outpatients may be given 300 mgm twice a week, or in some

stance

There is an active search for drugs that may be more regularly or rapidly effective than the sulfones, or that might be given in combination with them or that could be substituted when patients are not responsive or cannot tolerate the sulfones TB 1 has been found useful to a certain degree although it is not widely employed Ciba 1906 a thiourea derivative has been introduced for the therapy of leprosy This compound is well tolerated and has produced therapeutic responses in tuberculoid lepromatous and borderline cases including patients who have been resistant to sulfone treatment or who have had severe reactions to it

Prognosis The prognosis of untreated leprosy is generally unfavorable In the self healing benign cases crippling deformities often develop before the disease is overcome Lepromatous cases almost always deteriorate intermittently With modern treatment many benign cases are cleared up before the development of neural sequelae and many of the lepromatous type are rendered bacteriologically negative It must always be assumed however that deep seated bacilli still persist and that relapse may occur after treatment is suspended With modern treatment of secondary or concurrent conditions the death rates in leprosy institutions have decreased greatly

Prophylaxis and Control ... the

discovery and treatment of early

and some form of effective isolation

cases Prevention of contact with children is espec...

most areas it is not considered necessary to segregate "closed" cases These are treated in dispensaries but they cannot be regarded as entirely noninfectious and appropriate precautions must be taken in the home However under present day conditions the emphasis on segregation has been greatly reduced and the existence of special leprosy laws is deplored

It is possible but not proved that BCG inoculation of persons nonreactive to lepromin may be of value in prophylaxis by rendering such individuals reactive It is also a moot question whether family contacts should receive prophylactic sulfone medication

27

Plague

Synonyms Oriental plague pest black death

Definition Plague is an acute febrile infectious highly fatal dis ease which is characterized by inflammation of the lymphatics sep ticemia and petechial and diffuse hemorrhages into the skin [illegible] ous tissues and viscera It is freq [illegible]
often by [illegible]

Distrib [illegible]
to have [illegible] [illegible]
every imp [illegible] as invaded The more important
present en[illegible] ic centers appear in Table IV 12 and Figure IV 19

Etiology *Pasteurella pestis* (Yersin and Kitasato 1894) is a mem ber of the group producing hemorrhagic septicemias (pasteurellosis) in animals It is a short nonmotile gram negative bipolar-staining bacillus which exhibits marked pleomorphism and is often encapsulated Three general forms may be seen

1 Short rounded or oval often appearing as diplococci
2 Longer rods
3 Large oval or pear shaped or club shaped involution forms

Specific identification is based upon the morphology staining re actions cultural characteristics and the results of animal inoculation

Table IV 12 Principal Endemic Foci of Plague in Rodents

TYPE	LOCALITY
Murine plague (domestic rodents)	India
	China Manchuria Mongolia
	Burma
	Indonesia
	East Africa
	Madagascar
	West Africa
	South America Brazil Bolivia Peru Ecuador
Sylvatic plague (wild rodents)	United States western states
	China Mongolia
	Transcaucasia
	South Africa
	Argentina

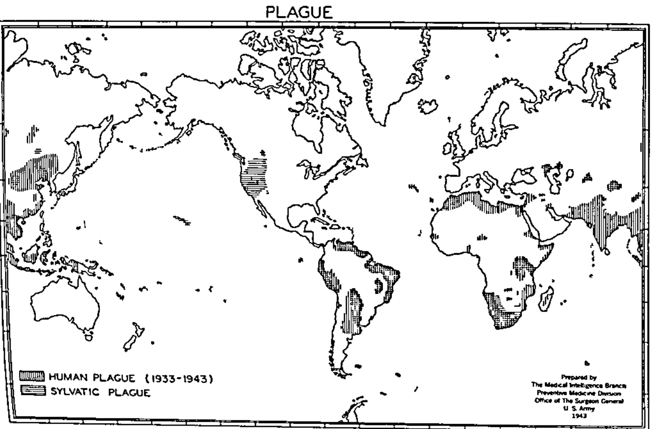


Figure IV 19 Geographic distribution of plague

Cultural Characteristics *Pasteurella pestis* grows equally well at 30° to 37° C This is of value for its isolation in pure culture and for identification On alkaline agar small translucent dewdrop colonies appear in 18 to 24 hours Acid without gas is formed from glucose maltose mannite and salicin Lactose is not fermented milk is not coagulated There is no indole production In bouillon under oil there is a characteristic stalactite growth extending downward from the surface Salt agar 2 5 to 3 5 per cent is useful for the production of involution forms which are of value in diagnosis

Animal Inoculation The guinea pig is the best laboratory animal for the recovery of these organisms since a single virulent bacillus produces fatal infection Inoculation should be made by rubbing into the shaved scarified skin of the abdomen If the inoculum contains plague bacilli death results in three to five days with the following characteristic findings

1 Marked subcutaneous edema congestion and hemorrhage about the site of inoculation

2 Buboes in one or both inguinal regions

3 Numerous yellowish white necrotic foci in the spleen and at times in the liver

4 Hemorrhages in the lungs and other tissues and occasionally in the heart muscle

5 Smears from the lesions and from the heart blood revealing large numbers of typical bipolar staining bacilli

Pasteurella pestis is easily killed by drying in sunlight and by ordinary disinfectants Its viability varies greatly in different environments

30 days
ouses in
13 days
corpses

the bacilli remain viable for prolonged periods

Rodents may frequently be found infected with bipolar staining bacilli which are difficult to differentiate from *P pestis* The more important of these are *P pseudotuberculosis rodentium* and *P aticada* (Table IV 13)

Epidemiology Although plague is a disease primarily of rats and other rodents in man it is one of the most fatal of all infectious diseases It occurs in three forms—bubonic primary septicemic and primary pneumonic Age sex race and occupation play no role in susceptibility Epidemics are usually bubonic but always include a small number of primary septicemic cases and cases of secondary plague pneumonia

The reservoirs of infection are rats and other rodents in which the disease occurs in acute subacute and chronic or latent forms Domestic rodents belonging to the family MURIDAE are primarily concerned in the infection of man Plague infection among the rat population is referred to as murine or rat plague and among wild rodents as sylvatic or wild rodent plague

Meteorologic conditions exert an important influence upon the epidemiology of the disease The gross climate is important in determining the survival of plague bacilli and the types of disease which they may

Table IV.13. Cultural Characteristics of *Pasteurella* Species*

	P pestis	*P pseudotuberculosis*	*P avicida*
Motility in 18 hour cultures at 22° C	−	+	−
Litmus milk	− or slight acid	Alkaline	−
Sugars	Acid in glucose, mal tose, mannitol and salicin	Acid in glucose, mal tose mannitol and salicin sometimes in sucrose	Acid in glucose man nitol and sucrose sometimes in mal tose
Indole	−	−	+
Methyl red	+	+	−
Methylene blue reduction †	−	+	+
Growth on MacConkey s agar	+	+	−
Pathogenicity to white rats	+	−	+

* From Wilson G S and Miles, A A Topley and Wilson's Principles of Bacteriology and Immunity 4th ed Baltimore, William Wood & Co, 1955

† Personal observations on a relatively few strains

produce in man Primary pneumonic plague epidemics rarely if ever occur in the absence of constantly low temperatures and high relative humidity Microclimate—the immediate environment of the flea—is of extreme importance in determining the life of the vector

Extreme heat and dryness are inimical to the spread of plague The disease is more commonly seen in the temperate zone in the summer and autumn months when fleas are most numerous and human disease in consequence often takes the bubonic form In India and other parts of the tropics the plague season frequently prevails during the cooler months of the year

Dissemination from one area to another may occur in a variety of ways but usually by the transportation of infected rats in ships Occasionally it may be by the importation of fleas in bales of material containing the infected and living insects Sometimes an ambulatory or more severe human case may be responsible In areas where sylvatic plague is present, migrations of the rodent population may extend the endemic area

Murine or rat plague is disseminated primarily by the brown sewer rat *Rattus norvegicus,* to the smaller domestic black house rat *R rattus rattus* The infected sewer rat not infrequently will enter the lower parts of buildings and die Immediately after its death the fleas leave the carcass in search of a new host to whom the infection is transmitted

Rattus r rattus is rare in Europe today but widespread and common in the tropics where it lives in close association with man *Rattus norvegicus* has a worldwide distribution *Rattus r alexandrinus* has been important in the epidemiology of plague in Egypt in the past and has been reported to be present in the South Pacific islands *Rattus hawaiiensis* is the reservoir in the Hawaiian Islands Rats in different areas apparently possess varying degrees of resistance to infection by the

plague bacillus The disease is transmitted from rat to rat and from rat to man by fleas

Sylvatic Plague Some 72 other rodents, of which the ground squirrel (Western United States) and the gerbille and the multimammate mouse (South Africa) are the most important, may act as reservoirs of the infection Sylvatic plague in wild rodents occurs in areas sparsely inhabited by man The rarity of human infections in the United States, even in the presence of marked epizootics, implies a weakness in the flea link of the transmission chain, since man is rarely infected unless directly exposed to fleas from rodent burrows or, more often, to contamination by handling infected animals The spread to a domestic rodent population, that is to say translation from sylvatic to murine plague, is most apt to occur when uncontrolled rodent populations come into contact and freely exchange their ectoparasites (Fig IV 20)

The Vector Various fleas are immediately responsible for transmission of the infection from the reservoir to man These insects may live for one to two years under favorable conditions of temperature and moisture They survive several months without food in cool and moist environments but die quickly in a hot dry climate In moderate temperatures they may remain infective for prolonged periods

A flea feeding upon its infected rodent host ingests the plague bacilli, which then multiply in its gut, sometimes becoming so numerous as to block the lumen Man may be infected by the bite of such an insect,

IV 14)

Table IV.14. Some Important Flea Vectors of *Pasteurella pestis*

FLEA	DISTRIBUTION	RESERVOIR HOSTS	TRANSMITS PRIMARILY TO
Xenopsylla cheopis	Widely disseminated	*Rattus rattus* *R norvegicus*	Rats and man
X brasiliensis	Uganda Kenya, Nigeria	Rats	Rats and man
X astia	India Ceylon, Burma, Mesopotamia, Mombasa	Rats	Rats
X nubicus	Tropical East and West Africa	Rats	*Rats*
X eridos	South Africa	Wild rodents	Wild rodents
Pulex irritans	Nearly cc	[illegible]	[illegible]
Nosopsyllus fasciatus	Tempera		
Diamanus montanus	Western		
Rhopalopsyllus cavicola	South An		
Ceratophyllus tesquorum	Russian steppes	Ground squirrels	Ground squirrels
Oropsylla silantiewi	Manchuria	Rodents	Rodents

Table IV.13 Cultural Characteristics of *Pasteurella* Species*

	P pesti s	*P pseudot berculos s*	*P av cada*
Motil ty in 18 hour cultures at 22° C	−	+	−
Litmus milk	− or sl ght acid	Alkal ne	−
Sugars	Acid in glucose mal tose mann tol and sal c n	Acid in glucose mal tose mannitol and salicin somet mes in s crose	Ac d in glucose man n tol and sucrose somet mes n mal tose
Indole	−	−	+
Methyl red	+	+	−
Metl ylene blue reduct on†	−	+	+
Growth on Mac Conkey s agar	+	+	−
Pathogen city to white rats	+	−	+

* From Wilson G S and Miles A A Topley and W lson s I rnciples of Bacteriology and Immunity 4th ed Baltimore William Wood & Co 1955
† Personal observat ons on a relatively few strains

produce in man Primary pneumonic plague epidemics rarely if ever occur in the absence of constantly low temperatures and high relative humidity Microclimate—the immediate environment of the flea—is of extreme importance *in determining the life of the vector*

Extreme heat and dryness are inimical to the spread of plague The disease is more commonly seen in the temperate zone in the summer and autumn months when fleas are most numerous and human disease in *consequence often takes the bubonic form* In India and other parts of the tropics the plague season frequently prevails during the cooler months of the year

Dissemination from one area to another may occur in a variety of ways but usually by the transportation of infected rats in ships Occasion ally it may be by the importation of fleas in bales of material containing *the infected and living insects Sometimes an ambulatory or more* severe human case may be responsible In areas where sylvatic plague is present migrations of the rodent population may extend the endemic area

Murine or rat plague is disseminated primarily by the brown sewer rat *Rattus norvegicus,* to the smaller domestic black house rat *R rattus rattus* The infected sewer rat not infrequently will enter the lower parts of buildings and die Immediately after its death the fleas leave the carcass in search of a new host to whom the infection is transmitted

Rattus r rattus is rare in Europe today but widespread and common in the tropics where it lives in close association with man *Rattus nor vegicus* has a worldwide distribution *Rattus r alexandrinus* has been important in the epidemiology of plague in Egypt in the past and has been reported to be present *in the South Pacific islands Rattus hawaiien sis* is the reservoir in the Hawaiian Islands Rats in different areas apparently possess varying degrees of resistance to infection by the

plague bacillus. The disease is transmitted from rat to rat and from rat to man by fleas.

Sylvatic Plague. Some 72 other rodents, of which the ground squirrel (Western United States) and the gerbille and the multimammate mouse (South Africa) are the most important, may act as reservoirs of the infection. Sylvatic plague in wild rodents occurs in areas sparsely inhabited by man. The rarity of human infections in the United States, even in the presence of marked epizootics, implies a weakness in the flea link of the transmission chain, since man is rarely infected unless directly exposed to fleas from rodent burrows or, more often, to contamination by handling infected animals. The spread to a domestic rodent population, that is to say translation from sylvatic to murine plague, is most apt to occur when uncontrolled rodent populations come into contact and freely exchange their ectoparasites (Fig. IV.20).

The Vector. Various fleas are immediately responsible for transmission of the infection from the reservoir to man. These insects may live for one to two years under favorable conditions of temperature and moisture. They survive several months without food in cool and moist environments but die quickly in a hot dry climate. In moderate temperatures they may remain infective for prolonged periods.

A flea feeding upon its infected rodent host ingests the plague bacilli, which then multiply in its gut, sometimes becoming so numerous as to block the lumen. Man may be infected by the bite of such an insect since *P. pestis* is regurgitated from the esophagus and proventriculus as the flea attempts to feed. The organisms are likewise passed in the feces of the flea and may infect man either through the bite wound or through a minute abrasion of the skin. It is possible that the body louse, *Pediculus humanus humanus*, and, more remotely, the bedbug *Cimex lectularius*, may occasionally transmit the infection directly from man to man (Table IV.14).

Table IV.14. Some Important Flea Vectors of *Pasteurella pestis*

FLEA	DISTRIBUTION	RESERVOIR HOSTS	TRANSMITS PRIMARILY TO
Xenopsylla cheopis	Widely disseminated	*Rattus rattus* *R. norvegicus*	Rats and man
X. braziliensis	Uganda, Kenya, Nigeria	Rats	Rats and man
X. astia	India, Ceylon, Burma, Mesopotamia, Mombasa	Rats	Rats
X. nubicus	Tropical East and West Africa	Rats	Rats
X. eridos	South Africa	Wild rodents	Wild rodents
Pulex irritans	Nearly cosmopolitan	Man, swine, rodents	Man, rodents
Nosopsyllus fasciatus	Temperate zone	*R. norvegicus*	Rats
Diamanus montanus	Western United States	Ground squirrels	Ground squirrels
Rhopalopsyllus cavicola	South America	Cavies	Cavies
Ceratophyllus tesquorum	Russian steppes	Ground squirrels	Ground squirrels
Oropsylla silantiewi	Manchuria	Rodents	Rodents



Figure IV 20 Epidemiology of plague

Other Means of Transmission Transmission of plague to man by other means is less common A small proportion of cases of bubonic plague may be traced to entry of the bacilli through abraded skin of the feet, as in cowdung floored houses in India, or of the hands in the performance of an autopsy or in handling or skinning infected animals

Primary septicemic plague may result from the entry of the bacilli

through mucous membranes especially those of the mouth throat and conjunctiva

Predisposing Factors Bubonic plague is commonly acquired through the bite of an infected human flea or rat flea Important contributory factors are an overcrowded human population housed in unsanitary buildings which provide adequate food and harborage for an uncontrolled rodent population Epidemics of bubonic plague are associated with a high incidence of the disease in rats with great mortality among them When the rodent population is sufficiently reduced many of the infected fleas migrate to man

A few severe epidemics of plague have been of the primary pneumonic type which is transmitted directly from man to man by droplet infection from the cough Meteorologic conditions particularly temperature are exceedingly important factors in determining the spread or failure to spread of the pneumonic type of the disease Freezing temperatures with high relative humidity favor transmission since pulverized and frozen sputum and cough droplets retain infective and virulent bacilli for long periods of time Communities in which there is over crowding of the population with close contact between sick and well and in which unsanitary conditions and practices are usual provide a fertile field for this type of the disease Isolated cases of secondary plague pneumonia occurring as a complication of bubonic or of primary septicemic plague often constitute the immediate origin of such an outbreak Such secondary pneumonia however is not as infectious as is primary

gitis lymphadenitis or bubo formation and bacteremia with metastatic localization

In bubonic plague the lymph nodes draining the site of infection are swollen edematous congested and hemorrhagic forming the primary bubo which often undergoes necrosis Adjacent nodes are matted together and there is much edema and hemorrhage in the surrounding tissues (Fig IV 21)

There are often secondary inflammatory changes similar in character in other lymph nodes in the body There is extensive damage to vascular and lymphatic endothelium which contributes to this process and to the development of cutaneous petechiae and hemorrhages in many parts of the body

There is marked visceral congestion involving the brain and the meninges as well as other organs The spleen is frequently enlarged to two or three times its normal size

Pneumonic Plague The pneumonia of plague is lobular in character extending to involve entire lobes There is intense congestion of the air passages with hemorrhagic exudate in the alveoli and bronchi but with little or no fibrin formation Great numbers of *P pestis* are present The bronchial and hilar nodes are involved and ecchymoses and fibrinous pleurisy may be present over the affected portion of the lung (Fig IV.22)



Figure IV.21. Section through plague bubo showing necrosis and beginning abscess formation, capsule of lymph node and surrounding edema and infiltration

Clinical Characteristics. The incubation period of bubonic plague is usually two to four days, less often as long as ten days. In primary pneumonic plague it may not exceed two to three days

Bubonic Plague. *Usually there is no prodromal period in bubonic* plague, although occasionally there may be a day or two of malaise and headache In the majority of instances the onset is abrupt with chill, rapidly rising temperature to 103° or 104° F, accompanied by rapid pulse and accelerated respiration A severe attack is usually attended by mental dullness, which is followed by anxiety or excitement The eyes are injected, the face congested, the tongue coated, and nausea and vomiting may be present Constipation is usual, the urine is scanty with moderate albuminuria An expression of intense anxiety is very characteristic of the disease In some instances maniacal delirium may occur, in others lethargy or coma, convulsions are common in children The acute stage with high fever commonly lasts two to five days, following which, in favorable cases, the temperature falls by slow lysis, reaching normal in about two weeks.

Definite bubo formation occurs in 75 per cent of cases, usually appearing from the second to the fifth day and preceded by local pain When fully developed the bubo may be the size of an egg and is hard and tender. In fatal cases it remains indurated, in others suppuration is common Incision, especially prior to the appearance of definite fluctuation, is hazardous because of the risk of initiating blood stream infection The common sites of the bubo are as follows

Inguinal	65 to 75 per cent
Axillary	15 to 20 per cent
Cervical	5 to 10 per cent

The acute stage is accompanied by a high leukocytosis which may reach 40 000 with a corresponding increase in the polymorphonuclear cells Positive blood culture is obtained in about 45 per cent of cases Death may occur within five days

Pestis Minor Mild ambulatory cases of plague with little or no fever or toxemia may be encountered Frequently there is a bubo in one groin less commonly on one side of the neck or in one axilla These may suppurate or may gradually be resorbed (Fig IV 23)

Primary Pneumonic Plague The onset of primary pneumonic plague is usually abrupt, with fever rising to 103° or 104° F within 24 to 36 hours True rigor is rare Painless cough and dyspnea appear within the first 24 hours The sputum at first is mucoid becoming blood

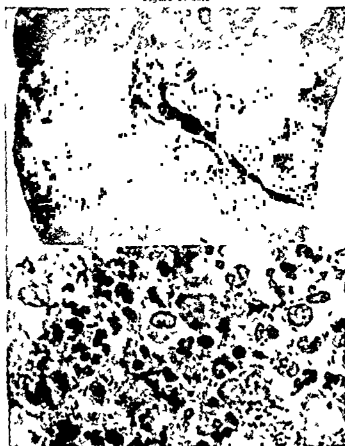


Figure IV 22A

Figure IV 22B

Figure IV 22. *Primary pneumonic plague A Confluent lobular pneumonia B Bacilli and exudate in alveolus.*



Figure IV.23 Pestis minor case of ambulatory plague showing axillary bubo (Courtesy of Dr A Macchiavello)

tinged but not tenacious in the fully developed case it is thin bright red and contains enormous numbers of *P pestis* Physical signs are often not marked even in advanced cases There is usually a high leukocytosis

Primary Septicemic Plague Septicemic plague can occur as a form of primary infection However a secondary septicemia occurs invariably in primary pneumonic cases and may occur in the course of bubonic plague In primary septicemia cerebral symptoms frequently develop with great rapidity and intensity rapidly progressing to coma This form of the disease if untreated is fatal Death occurs usually within three days of onset and frequently before there is demonstrable enlargement of superficial lymph nodes

Diagnosis The clinical picture of sudden onset of high fever marked toxemia lymphadenitis extreme anxiety and high leukocytosis is suggestive The appearance of a bubo is important supporting evidence However in primary septicemic plague there may be no significant clinical signs and in primary pneumonic plague physical signs over the chest may be trivial even in the presence of enormous numbers of bacilli in the sputum

The definitive diagnosis depends upon the demonstration and identification of *P pestis* In bubonic cases material aspirated from the bubo should be stained by Gram s method and examined for the characteristic bipolar pleomorphic bacilli In septic and pneumonic cases smears of blood and sputum should similarly be examined The results of culture and animal inoculation are too delayed to permit the early diagnosis essential for effective treatment

All material suspected of containing *P pestis* must be handled with extreme care Inoculated animals must be free from fleas and maintained under strict quarantine in insect free cages All individuals

cages,

must be

Differential Diagnosis In the early stages of the disease certain of the clinical types may be confused with typhus fever, relapsing fever, malaria, dengue, tularemia and rarely with typhoid

Prognosis. Untreated, or inadequately treated, primary pneumonic and septicemic plague are generally fatal diseases In the past, the mortality from bubonic plague has varied from 60 to 90 per cent Since the introduction of the sulfonamide drugs and the antibiotics the mortality has been reduced remarkably In India, streptomycin lowered the fatality rate of bubonic and septicemic plague to 10 per cent

Treatment. Streptomycin is the drug of choice for the treatment of all forms of plague It should be administered intramuscularly in the following dosage 0 5 gram every three or four hours until the temperature becomes normal, thereafter 1 0 gram daily in divided doses until a total of 15 0 grams has been given

In severe cases, Aureomycin, oxytetracycline (Terramycin) or chlor-

dosages are advised sulfadiazine initial dose 4 0 grams followed by doses of 1 5 to 2 0 grams every four hours for ten days

Surgical Treatment of Bubo Hot wet applications may hasten localization Incision should be avoided until frank fluctuation occurs

Prophylaxis. Prophylaxis against plague is accomplished (1) by strict isolation of the sick, (2) by appropriate sanitary measures, and (3) by protection of the individual

1 *Isolation of the Sick* Strict isolation of the patient in a separate insect proof room is essential All waste articles possibly contaminated and all discharges from the patient should be burned or otherwise satisfactorily disinfected Bodies of humans and animals dead from plague should be disposed of with extreme sanitary precautions A room previously occupied by a patient with plague must be completely and thoroughly cleaned and treated with DDT residual spray or powder (see Table XI 10, p 774)

In the presence of pneumonic plague or when its presence is suspected, physicians, nurses and any others in contact with the patient or entering the patient's room must be protected by complete coveralls, gloves and hoods equipped with goggles or plastic face pieces Contacts or suspected contacts should be treated with DDT dusting powder and should be segregated Their temperatures should be recorded daily Sulfadiazine or sulfamerazine 3 0 grams daily, should be given for at least five days after the last exposure Streptomycin is not recommended for prophylactic purposes because of the rapid excretion and the difficulties of

repeated dosage It should however, be given immediately if suggestive symptoms develop

2 *Sanitary Measures* The general sanitary measures directed toward the prevention or control of plague are concerned primarily with rat and rat flea eradication

Importation of rats from an endemic area should be guarded against by rat proofing of ships application of measures to prevent rats from leaving ships and appropriate fumigation by cyanide gas

In towns and cities buildings should be rat proofed and natural harborages especially rubbish refuse and garbage eliminated Trained personnel should be utilized in well organized programs to distribute the highly effective rodenticides sodium fluoroacetate (1080") and dicoumarin (Warfarin) Other poison baits using red squill thallium sulfate zinc phosphide or barium carbonate may be used but these are generally considered less effective than "1080 or Warfarin

All rats obtained should be systematically examined for the presence of *P pestis* in their ectoparasites and in their viscera Examination of rats found dead is of great importance since rodent epizootics commonly precede the appearance of plague in man

In the control of outbreaks or epidemics of human plague the destruction of rat fleas is of major importance (see Table XI 10 p 774) DDT (10 per cent in pyrophyllite) has proved highly effective for this purpose The powder should be dusted extensively in and around houses as well as in clothing bedding and house furnishings The eradication program must be energetic and prompt and must be directed by personnel who are familiar with current epidemiologic control measures

Clothing and personal effects of passengers at ports of departure from an active plague area and departing vehicles and aircraft should be thoroughly dusted with DDT dusting powder

3 *Personal Prophylaxis* In the presence of an outbreak all possibly exposed persons should be vaccinated Vaccination confers immunity for four to six months the degree of which is still uncertain The two dose heat killed vaccine has been used extensively However the single dose vaccine composed of living avirulent plague bacilli has been observed to reduce the attack rate markedly

The use of DDT dusting powder and the sulfonamide drugs after contact with septicemic or pneumonic cases has been discussed above

Personnel engaged in rat control programs should be immunized and should wear flea proof DDT dusted clothing with particular emphasis on high boots tight wristbands and tight collars This insures maximum protection against fleas found on the rodents and present abundantly in their burrows and nests

28

Cutaneous Diphtheria

John P O Brien

Distribution This infection has been reported especially from Palestine North Africa India and Burma

Clinical Characteristics Cutaneous diphtheria may be primary or secondary Secondary invasion by the diphtheria bacilli may occur in wounds wound diphtheria and in any other skin lesion such as a burn insect bite tropical ulcer or even an eczematoid rash The clinical features are pleomorphic The infection should be watched for even in the absence of flare up of the primary lesion necrosis or membrane formation

Primary cutaneous diphtheria on the other hand is rather characteristic It affects the extremities principally although it is not confined to them and there may be a history of mild trauma The most typical lesion is a round or oval ulcer measuring 1 to 3 cm in diameter Vesicles or pustules are sometimes seen in early stages

The ulcer is shallow with rolled bluish tender edges and characteristically is covered by an adherent membrane or more often by a hard dark scab (eschar) An adjacent bulla may be present After a week or more the eschar separates leaving a shallow punched out ulcer with a flat unhealthy floor Multiple lesions are common

Pain is generally present at first but later there may be anesthesia a helpful point in diagnosis Healing is from the periphery and is exceedingly slow The resulting scar is thin and depressed It may break down repeatedly before healing is complete

Infections (or the carrier state) in the throat or nose may be associated but are not invariable

During the prolonged course of four months or more one should watch for neurologic and cardiac complications Weekly electrocardiographic tracings should be made if possible

Diagnosis Diagnosis depends upon bacteriologic examinations with culture on selective media The inoculum must be taken from the deep aspect of the eschar or membrane Virulence tests are usually necessary for confirmation of cultures

Treatment Immediate isolation bed rest and proper nursing care in a hospital for at least five weeks are essential After previous intracutaneous testing for sensitivity and desensitization if required diphtheria antitoxin should be given intramuscularly in doses of 20 000 to

40 000 units Palliative measures include use of the antibiotics and simple antiseptics locally for control of secondary pyogenic infections

Prophylaxis Schick positive contacts should be immunized with antitoxin In an epidemic others who are Schick positive should be immunized with diphtheria toxoid

29

Tularemia

Revised by Paul D Ellner

Synonyms Plaguelike disease of rodents deer fly fever rabbit fever

Definition Tularemia is a bacteremic plaguelike disease of various small mammals especially rabbits and hares caused by *Pasteurella tularensis* (*Bacterium tularense*) It is highly infectious In man it is characterized by an ulcer at the site of inoculation regional lymphadenitis and severe constitutional symptoms

Distribution The disease occurs in the United States Canada Alaska Norway Sweden Germany Austria Czechoslovakia Turkey Russia and Japan

Etiology *Pasteurella tularensis* is a small pleomorphic gram negative nonmotile non spore bearing aerobic bacillus Stained smears exhibit coccoid bacilli and bipolar stained bacillary forms It grows well on blood dextrose cystine agar and coagulated egg yolk media but not on plain agar or other ordinary media

Epidemiology *Pasteurella tularensis* is widely distributed in nature in a variety of animal hosts the more important of which are wild rabbits and hares Among these it is transmitted by blood sucking arthropods such as ticks fleas lice and flies Other animals infected include ground squirrels wild rats meadow mice the opossum beavers and water rats Less frequently it occurs as an epizootic in certain game birds particularly quail and grouse

Ticks belonging to the genera *Haemaphysalis* and *Dermacentor* are most important vectors of the disease among mammals and birds In these arthropods the infection is transmitted transovarially from one generation to another Species of *Ixodes* are likewise active in transmission among rabbits Passage of the infection through the ova however has not been demonstrated for this genus

The infection reaches man by a variety of means which may be loosely

classified as contaminative inoculative and ingestive Infection by contamination may occur through minor abrasions of the skin or even the unbroken skin and mucous membranes by the handling skinning and dressing of diseased animals or birds and by contact with the feces of infected ticks which contain the organisms

Infection by inoculation is acquired by the bite of infected ticks particularly *D andersoni* and *D variabilis* the deer fly *Chrysops discalis* and other blood sucking arthropods Bites or scratches by diseased animals may likewise cause infection

Tularemia may also be acquired through the ingestion of insufficiently cooked meat and rarely contaminated water

Although *P tularensis* has been demonstrated in the sputum from human cases of the disease there is no record of direct spread from man to man

Pathology In the acute form of the disease a primary ulcer develops at the site of inoculation accompanied by lymphangitis and regional lymphadenitis The affected lymph nodes may become considerably enlarged closely resembling the bubo of plague and often undergo necrosis and suppuration Focal necroses occur in the spleen liver and lungs with infiltration by polymorphonuclear leukocytes and large mononuclear cells In some instances there is a lobular pneumonia with an exudate containing many monocytes The organisms rarely can be demonstrated in the tissues

The subacute form of the disease is characterized by tuberculoid lesions in various organs These present a central zone of focal necrosis enclosed by epithelioid cells and fibroblasts surrounded by small lymphocytes Occasional giant cells are present

Clinical Characteristics The various clinical phenomena of tularemia tend to divide the disease into four distinct clinical types

1 The ulceroglandular type
2 The oculoglandular type
3 The glandular type
4 The typhoidal type

These have much in common being distinguished one from the other by certain particularly prominent features

The incubation period in the majority of cases varies from three to five days and is terminated by abrupt onset of acute disease without antecedent prodromal symptoms frequently accompanied by severe headache sharp chill and rapid rise of fever to 103° or 104° F There is frequently a one to three day remission of fever accompanied by amelioration of constitutional symptoms in the first week of the disease This is followed by return of the pyrexia and other phenomena The acute phase is self limited and usually lasts two to three weeks During this period recurring chills drenching sweats marked prostration aching pains in the back and extremities severe headache and vomiting are often prominent features There is a moderate leukocytosis seldom exceeding 15 000 Various types of skin eruption may occur Defervescence is by lysis

1 *Ulceroglandular Type* This includes about 84 per cent of cases The primary lesion commonly occurs on the hands or fingers Usually within 48 hours of the onset a painful regional lymphadenitis develops preceding the appearance of an inflamed papule at the site of inoculation (Fig IV 24) This progresses to pustule formation and subsequently to the development of a punched out ulcer which heals with considerable scarring A superficial lymphangitis between the primary lesion and the enlarged regional lymph nodes is common and nodular swellings along the course of the inflamed lymphatics may be suggestive of sporotrichosis The epitrochlear and axillary lymph nodes are most frequently involved Suppuration occurs in about 50 per cent of cases in the others resolution is slow and may require several months

2 *Oculoglandular Type* This type includes about 6 per cent of cases

3 *Glandular Type* This form of tularemia comprises about 4 per cent of cases It is characterized by a regional lymphadenitis but there is no lesion at the site of infection

4 *Typhoidal Type* This type includes about 5 per cent of cases

Complications Bronchopneumonia bronchitis and pleurisy with or without effusion may occur as complications In the presence of pulmonary involvement *P tularensis* may be recovered from the sputum Other serious complications are blindness following the oculoglandular type *P tularensis* septicemia and meningitis

Prognosis Without adequate treatment the mortality is approximately 7 4 per cent

Diagnosis The clinical picture and a history of contact with wild rabbits or other rodents or of bites by ticks or deerflies should be suggestive of tularemia The fever rises sharply with a temporary remission followed by a febrile period of two to three weeks duration Local lesions such as ulcer enlarged lymph nodes or conjunctivitis may not be present during the first few days Definitive diagnosis is reached by recovery of the organism Blood cultures should be made on dextrose cystine agar or thioglycolate blood agar Positive cultures may likewise be obtained from primary lesions material aspirated from softened lymph nodes or the sputum (Fig IV 24) Inoculation of suspected material into guinea pigs is a useful diagnostic procedure since these animals are susceptible and usually die within a week The gross lesions closely resemble those of plague but are distinguishable by histopathologic examination and by culture The failure of *P tularensis* to grow on plain agar and the characteristic morphologic variants of *P pestis* on salt agar permit easy differentiation Inoculated animals can also be used for agglutination tests

Demonstration of a rising agglutinin titer in the patient s serum during the course of the disease is significant Antibiotic treatment does not affect the rise of titer sufficiently to interfere with diagnosis

The diagnosis of the typhoidal or pneumonic type may be difficult Suspected cases particularly in endemic areas or among laboratory workers exposed to infection should be treated promptly

Differential Diagnosis Inflammatory nodules along the superficial lymphatics in the ulceroglandular type may suggest sporotrichosis The glandular type particularly may be confused with plague and in the presence of inguinal lymphadenitis pyogenic infections venereal bubo and climatic bubo must be considered as well The frequent cross agglutination with *Br abortus* and *Br melitensis* may be misleading However as the disease progresses the agglutinin titer for *P tularensis* far exceeds the titer for the *Brucella* group

Treatment Streptomy ... of
cho ce for the treatment of ... en
reported with Aureomycin ... re
lapses are said to be more (

Streptomycin or dihydrostreptomycin should be administered intramuscularly A total of 2 0 to 4 0 grams given in individual doses of 0 5 gram every eight hours is usually sufficient to effect a cure except in the typhoidal type of the disease Other recommended regimens are 0.5 gram daily for two days followed by 0 25 gram daily for four days or 0 5 gram daily for six days

In the typhoidal type of tularemia the antibiotic should be continued until the patient is afebrile

Defervescence usually occurs within three days except in the typhoidal type of the disease Antibiotic therapy early in the clinical course may inhibit natural immunity so subsequent reinfection may occur

Prophylaxis The essential feature of the prophylaxis of tularemia is avoidance of the reservoir hosts In heavily endemic areas rabbits and other rodents should be handled with caution since *P tularensis* may be present not only in the animal itself but in tick feces in its fur When ticks are prevalent suitable precautions should be taken including the wear



Figure IV.24 Tularemia primary lesion on hand.

ing of protective clothing and the prompt removal of ticks before their attachment Trouser legs should be tucked into boots and insect repellent (612 or dimethyl phthalate) applied generously to the boot tops and trousers below the knees Gloves and shirt sleeves may be similarly treated (Table XI 10, p 776) It is highly important that the body be carefully inspected at the end of the day and all ticks removed

Prophylactic vaccination has proved effective for the prevention of tularemia among laboratory workers exposed to these organisms It is to be recommended for those exposed to tularemia as an occupational hazard if precautions are taken to exclude hypersensitive persons

Wild birds and game used for food must be thoroughly cooked The usual methods for water purification confer protection against the rare water borne infections

V

Mycotic Diseases

Norman F Conant

30

Introduction

The superficial and the systemic mycoses form a group of diseases resulting from infection of the skin or the viscera by pathogenic fungi Although many of these agents are widely spread geographically, they have greatest importance in the tropics where the conditions of climate and sanitation provide an especially favorable environment

The fungi belong to a subdivision of the plant kingdom known as the THALLOPHYTA These are characterized by a simple filamentous structure without differentiation into roots, stems and leaves The THALLOPHYTA in turn are subdivided into the ALGAE, which contain chlorophyll, and the FUNGI, which lack chlorophyll and which are, therefore, parasitic or saprophytic in character These latter include the SCHIZOMYCETES, or bacteria, the MYXOMYCETES, or slime moulds, and the EUMYCETES, or true fungi (Fig V 1)

vegetative body composed of filamentous elements or hyphae, and reproductive organs or spores of various types produced in various ways Final identification of the fungi requires cultivation on artificial media and study of the gross colony, the hyphae, the method of spore formation, and the type of spores produced

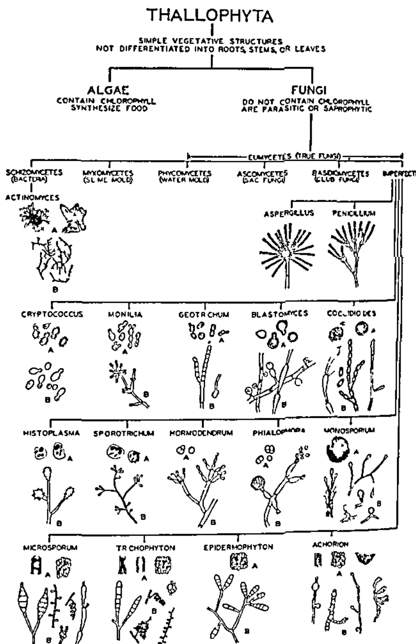


Figure V.1 Classification of the THALLOPHYTA Forms labeled A—forms occurring in the pathologic lesion forms labeled B—forms occurring in culture (After Musser Internal Medicine Its Theory and Practice Philadelphia Lea & Febiger 1938)

31

Cutaneous Mycoses

The dermatomycoses are superficial infections of the skin or a
pendages caused principally by members of three closely related g
of the FUNGI IMPERFECTI—*Trichophyton*, *Microsporum* and *Epidermo*
ton. They do not invade the deeper tissues or the internal organs. M
bers of the genus *Trichophyton* attack the hair, the skin and the n
The fungus may be confined to the cortex of the hair appearing as cha
of spores arranged in parallel rows or it may be on the surface of t
hair in chains of small (microspore type) or large (macrospore type
spores. In the skin and the nails these fungi present segmented branch
ing mycelial elements with or without chains of spores and are dis
tinguishable from *Microsporum* and *Epidermophyton*.

The genus *Microsporum* attacks the hair and the skin. Infected hairs
from the scalp commonly present a characteristic appearance produced
by a sheath of small spores surrounding the shaft of the hair and tending
to be in a mosaic arrangement rather than in parallel rows as in *Tricho*
phyton infections. In the skin species of *Microsporum* form segmented
mycelial elements which are identical in appearance with those of
Trichophyton and *Epidermophyton*.

The genus *Epidermophyton* attacks the skin and nails forming seg
mented branching mycelial elements which are indistinguishable from
those of *Microsporum* and *Trichophyton* (Table V 1).

Diagnosis of Dermatomycoses. A diagnosis of dermatomycosis
may be made by direct microscopic examination of an infected hair
or of scrapings from the margins of lesions of the skin or nails. Although
a clue to the particular genus may be obtained by such examination in
the case of *Trichophyton* or *Microsporum* infections of the hair, definitive
diagnosis can be made only by examination of the growth characteristics
in artificial culture media. Since the morphology of all three genera in
infected skin and nails is identical, differentiation and species identifica
tion must be based entirely upon the cultural characteristics.

Microscopic Examination. For the microscopic examination of
scrapings from the skin or nails or fragments of hair, the material should
be placed in a drop of 10–40 per cent potassium hydroxide on a clean
microscope slide covered with a coverglass and heated gently. If clearing
is not adequate, additional potassium hydroxide may be run in under
the coverglass and the preparation reheated. Following such treatment
the mycelia and spores are easily distinguished (see p 802).

Table V.1. Mycotic Infections of the Skin and Appendages

DISEASE	ETIOLOGIC AGENTS
Tinea capitis	*Microsporum audouini* *M canis* *M gypseum* *Trichophyton mentagrophytes* *T violaceum* *T schoenleinii* *T sulfureum* *T tonsurans*
Tinea favosa	*T schoenleinii* *T violaceum* *M gypseum*
Tinea barbae	*M canis* *T rubrum* *T mentagrophytes* *T verrucosum*
Dermatophytosis	*Trichophython* species *Epidermophyton floccosum* *Candida albicans*
Tinea cruris	*E floccosum* *Trichophyton* species
Tinea circinata (corporis)	*Trichophyton* species
Tinea imbricata	*T concentricum*
Tinea versicolor (pityriasis versicolor)	*Malassezia furfur*
Otomycosis	*Aspergillus* species *Penicillium* species *Candida* species

Cultures Similar material should be used for culture Hair or scrapings should be placed between two slides previously wrapped in paper and sterilized After rewrapping the material may be transported to the laboratory for immediate inoculation on Sabouraud's glucose agar to which ten units of penicillin and 30 units of streptomycin per milliliter of agar have been added Such a medium will inhibit bacterial growth Also, actidione may be added (0 1 mgm /ml) to the above medium to inhibit saprophytic fungus growth All cultures should be maintained at room temperature for two to three weeks Differentiation of the genera and identification of the species are based upon the gross and microscopic characteristics of the colonies and their elements

Tinea Capitis

Synonyms Tinea tonsurans herpes tonsurans ringworm of the scalp

Definition A fungus infection of the stratum corneum of the scalp and the hair most common in children characterized by scaling occasionally dermatitis and breaking of infected hairs it usually disappears spontaneously at puberty

Distribution This infection is widespread without geographic limitations and may occur epidemically in schools and among crowded populations

Etiology Tinea capitis is produced by several species of *Microsporum* and *Trichophyton*

Pathology The fungus first invades the stratum corneum of the scalp producing a minute rounded scaling patch or a reddish papule from which a hair projects Subsequently there is invasion of the hair follicle and then the deeper or superficial portions of the shaft of the hair More severe reactions lead to kerion formation and an edematous pustular infection of the scalp

Clinical Characteristics. The infected hairs become lusterless and brittle and finally break leaving short stubs projecting from the lesion Temporary or permanent alopecia may result The more severe infection or kerion is a painful weeping pustular infection with crusting

Diagnosis Microscopic examination of a potassium hydroxide preparation of scrapings from the scalp or of the hair is done initially to detect the presence of fungi Cultures should be made and the etiologic agent specifically identified

Treatment. Treatment is difficult and often unsatisfactory but spontaneous recovery usually follows an inflammatory reaction to the infection The scalp should be shampooed daily with soap and water to remove all crusts and scales after which local agents such as propionate caprylate compound ointment (Sopronol) 5 per cent undecylenic acid ointment (Desenex) salicylanilide ointment or 5 per cent ammoniated mercury ointment should be rubbed into the scalp X ray epilation although considered the most direct method of treatment should not be attempted in the presence of inflammation or until a trial of three to four months of local treatment has proved unsatisfactory Manual epilation of infected hairs and crusts is helpful If secondary infection is present warm saline compresses may be necessary Three per cent sulfur and 3 per cent salicylic acid in petrolatum may be substituted for the ammoniated mercury as an adjunct Personal effects such as combs and hair brushes caps or hats must be sterilized and should not be used by others

Griseofulvin is an orally administered antibiotic that has recently been found to be a specific drug for the treatment of infections caused by the dermatophytes *Trichophyton* *Microsporum* and *Epidermophyton* The daily dose is 1 0 gram but the optimum has not yet been established

Tinea Favosa

Synonym. Favus

Definition. A fungus infection of the scalp of the non hairy skin of the body or of the nails commonly seen in children It may extend into adult life, it is characterized by the formation of yellowish crusts over lying shallow ulcers

Distribution. Classic favus is common in China and central Asia It is not uncommon in North Africa, the Balkan region Germany and Mexico The disease is rare in other areas As is the case with tinea capitis, it may occur epidemically

Etiology. This condition is usually caused by *Trichophyton schoenleinii* (Fig V 2)

Clinical Characteristics. The initial lesions appear as minute whitish, scaly patches, subsequently sulfur colored crusts are produced piling up to form an elevated mass with raised edges These crusts are very adherent Removal reveals a superficial ulcer oozing serum or blood tinged exudate This infection may cause permanent alopecia

Diagnosis This may be obtained by microscopic examination of a potassium hydroxide preparation of scrapings from the early lesions and identification of the fungus by culture

Treatment. The methods advised for tinea capitis should be used Roentgen epilation is almost always necessary However Griseofulvin has been shown to give excellent curative effects and should be used

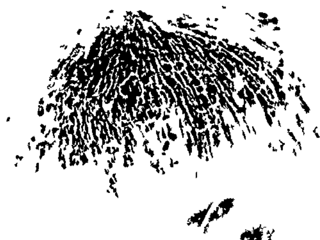


Figure V 2 Favus showing alopecia and crusted lesions of scalp

Tinea Barbae

Synonyms Tinea sycosis barber's itch ringworm of beard

Definition A fungus infection of the skin hair and hair follicles usually resulting in a chronic deep suppurative lesion men involving the skin hair and hair follicles of the bearded area and neck of

Distribution This infection is widespread without geographic limitations but may occur in small epidemics as a result of contact with infected cattle

Etiology Tinea barbae is produced by *Trichophyton mentagrophytes T rubrum T violaceum* and *Microsporum canis* Infection from cattle can be caused by *T mentagrophytes* or *T verrucosum* The latter is difficult to isolate on standard media

Pathology Superficial infection of the skin produces scaling circular lesions with a vesiculopustular border Deep infection of the skin produces suppurative lesions with follicular pustules kerion formation and extensive abscess formation

Clinical Characteristics The superficial lesions resemble those of tinea circinata of the glabrous skin (Fig X 10 p 226) Progressive infection may lead to a suppurative folliculitis forming large nodular crusted lesions which extrude pus on slight pressure The infected hairs are brittle and easily removed few are seen in older lesions

Diagnosis Microscopic examination of potassium hydroxide preparations of skin and hair should reveal fungus elements Cultures of such material are necessary to determine the etiologic agent of a given case

Treatment Early superficial lesions may be treated successfully with 3 per cent ammoniated mercury or tincture of iodine Treatment of chronic suppurative lesions is difficult Compresses twice daily for one half hour with Burow's solution (1 15) Vleminck's solution (1 33) or hypertonic saline solution may be helpful Hairs in the affected area should be manually epilated Antibiotics and or sulfonamides should be used to control secondary bacterial infections and the antibiotic griseofulvin used for specific treatment

Dermatophytosis

Synonyms Trichophytosis epidermophytosis ringworm of hands and feet Hong Kong foot athlete's foot

Definition Dermatophytosis is a chronic superficial infection of skin especially of that between the toes with maceration and cracking occasionally extending to involve adjacent skin areas Less com



Figure V 3 Dermatophytosis of foot early lesions scaling of skin of toes (Courtesy Dr Ray O Noojin Duke University)

monly it may affect the hands groins axillae and other regions It is accompanied by intense itching (Fig V 3)

Distribution The infection is widespread and may be particularly troublesome in the moist tropics and subtropics

Etiology It is usually due to a species of *Trichophyton* or less commonly *Epidermophyton floccosum* or *Candida albicans*

Epidemiology This infection is extremely common and widespread The fungi are resistant and persist indefinitely in shoes and other contaminated leather objects They may be transmitted by towels and clothing unless these are sterilized They frequently contaminate the floors of baths and washrooms The infection is acquired directly from contact with an infected individual or indirectly from contaminated floors and articles of clothing A hot humid climate and wet feet are predisposing factors

Pathology The infection is limited to the cornified layer of the skin producing acute chronic and hyperkeratotic lesions The acute stage is accompanied by erythema scaling and cracking of the affected skin Secondary infection is common Invasion of the nails (onychomycosis) is frequent

Remote skin sensitization may occur and be accompanied by eruptions dermatophytids on various parts of the body These do not contain the fungi and subside with control of the active focus

Clinical Characteristics The interdigital areas especially between the third and fourth and fourth and fifth toes are the usual sites of infection The lesion may consist of simple erythema with scaling Fissuring between the toes is common and the process may be complicated by secondary bacterial infection In chronic infections the skin is thickened white and macerated Not infrequently deep shotty vesicles appear on the soles of the feet and the palms of the hands These are accom

panied by pruritus and contain clear mucoid material In severe cases eczematoid lesions may occur involving the foot, ankle, groin, axilla, *hand and other areas These may present an acute inflammatory process* with edema and cellulitis due to secondary bacterial invasion (Figs V 4, V 5) Less commonly there may be involvement of the perianal skin with severe pruritus

Involvement of the nails, especially the toenails is frequent, and characteristically one or more escape invasion The affected nail becomes deformed, discolored, opaque and friable Onychomycosis is resistant to therapy and consequently constitutes an important reservoir for reinfection (Fig V 6)

The remote skin rashes or dermatophytids are considered to be an allergic reaction following upon cutaneous sensitization to the fungus The lesions are not distinctive and may be acute, chronic or eczematoid in nature They usually appear immediately following a flare up of the infection between the toes (Fig V 7)

Diagnosis. It is extremely important to make a careful examination of the skin between and beneath the toes Scrapings should be made from the margin of the lesion with a sharp scalpel Microscopic examination of the potassium hydroxide preparation of this material or



Figure V 4



Figure V 5

Figure V 4 Dermatophytosis of foot advanced lesions showing undermining bullous response with vesicles and pustules (Courtesy Dr Ray O Noojin, Duke University)

Figure V 5 Dermatophytosis of hand (Courtesy Dr J Lamar Callaway Duke University)

Figure V 6





Figure V 7

Figure V 6 Onychomycosis invasion of the nails (Courtesy Dr J Lamar Callaway Duke University)

Figure V 7 Dermatophytid of hands (Courtesy Dr J Lamar Callaway Duke University)

of the epithelial covering of vesicles will reveal the mycelia of the fung
Cultures should be made for specific identification of the fungus (p 111

Treatment The commonest error in the therapy of both acute and chronic dermatophytosis is *overtreatment* which frequently produce severe dermatitis There is no standardized or universally successful method of management Treatment must be individualized for each case Roentgen therapy is not fungicidal but is useful in the control of the eczematoid complications

Chronic Stages For the chronic stages the recommended meas ures are as follows

1 Daily 1 4000 potassium permanganate soaks for one half hour followed by mechanical debridement of all of the crusts scales and dead skin

2 One half strength Whitfield's ointment propionate caprylate com pound ointment (Sopronol) 5 per cent undecylenic acid ointment (De senex) or salicylanilide ointment should be applied overnight *The excess should be removed the following morning* followed by the application of

3 Fifteen per cent calcium propionate talcum powder (Sopronol) or Desenex powder for daytime use

4 One per cent iodine and 3 per cent salicylic acid in 70 per cent alcohol may be used at night instead of one half strength Whitfield's ointment

5 Castellani's paint may be used at night instead of the one half strength Whitfield's ointment

Severe Cases with Eczematoid Lesions None of these fungicidal preparations should be used in the presence of acute eczematoid lesions or with secondary bacterial infections They should be treated by bed rest elevation of the affected parts and wet dressings of saturated boric acid solution or Burow's solution diluted 1 20 After the acute process has been controlled the treatment regimen outlined above may be started cautiously beginning with greatly reduced concentrations

Onychomycosis Treatment of onychomycosis is exceedingly un satisfactory and surgical avulsion is not recommended Daily filing of the nails to tissue paper thinness followed by 1 4000 potassium per manganate soaks for one half hour after which 10 per cent sulfur and 10 per cent salicylic acid in petrolatum is rubbed in will sometimes effect a cure Filtered roentgen therapy in fractional doses (75 r) at weekly intervals for four to six weeks may help further with the control of the onychomycosis

Dermatophytids The treatment of dermatophytids is symptomatic ut eventual cure depends on control of the active fungus focus

Prophylaxis The prophylaxis of dermatophytosis consists of care l drying of the skin especially between the toes the use of slippers public baths and washrooms the avoidance of borrowed clothing d proper sterilization of clothing including socks and towels The ular use of a foot powder consisting of calcium propionate 15 per nt in a talc base is a highly efficient prophylactic measure

Tinea Cruris

Synonyms Dhobie itch eczema marginatum ringworm of the groin crotch itch jock itch

Definition Tinea cruris is a superficial fungus infection of the skin primarily of the upper and inner aspects of the thighs In severe cases it may extend to involve adjacent skin areas and the axillae

Distribution The infection is widespread without particular geographic limitation

Etiology. It is commonly due to infection by *Epidermophyton floccosum* less commonly by species of *Trichophyton*

Epidemiology Heat humidity excessive perspiration and friction from clothing are predisposing causes Indirect transmission occurs through the use of unsterilized towels and borrowed clothing

Clinical Characteristics Tinea cruris is characterized by brownish or reddish lesions having a scaly surface and presenting a papular or finely vesicular border These spread peripherally and tend to clear in the center Small satellite lesions are not infrequent The infection may extend to adjacent areas particularly the scrotum perineum and lower abdomen and in severe cases the axillae may be involved (Figs V 8 V 9)

Diagnosis The diagnosis of tinea cruris is based in part upon the appearance and distribution of the lesions and in part upon the microscopic examination of potassium hydroxide preparations of scrapings from the margin of an active lesion Such examination will reveal the mycelia of the fungus Specific identification requires examination of cultures (See *Diagnostic Methods* p 824)

Treatment The recommended measures are as follows

1 1 4000 potassium permanganate sitz baths or compresses at night followed by

2 Castellani s paint or one fourth to one half strength Whitfields ointment or sodium propionate ointment

3 Pragmatar ointment may be used instead of No 2

4 Fifteen per cent calcium propionate in talcum should be used during the daytime

5 Extreme cleanliness is absolutely necessary

6 The affected areas should be kept as dry as possible during the daytime Cool loose fitting clothing is helpful

7 Griseofulvin has become the drug of choice in extensive infections

It is important to remember that strong fungicidal preparations should not be used on the scrotum or in the vicinity of the anus In the presence of an active inflammatory process fungicidal preparations should not be used until the inflammation has been completely controlled by wet boric acid or 1 20 Burow s solution dressings

Prophylaxis The prophylaxis of tinea cruris consists of the avoidance of borrowed clothing the proper sterilization of towels and laundry and the use of dusting powder consisting of calcium propionate 15 per cent in a talc base



Figure V 8 Tinea cruris showing marginat on and scat ered active foci which may later coalesce (Courtesy Dr J Lamar Callaway Duke Un vers ty)



V.9 Tinea cruris active serpiginous border sharply marginated (Courtesy Dr J Lamar Callaway Duke University)

Tinea Circinata

Synonyms. Tinea corporis, tinea glabrosa, trichophytosis, "ringworm" of the body.

Definition. Ringworm of the body is a superficial fungus infection with granulomatous or generalized encrusted lesions frequently accompanied by pruritus

Distribution. This infection has a widespread distribution but is more common in the tropics and subtropics than in the temperate zones

Etiology. It is due to infection of the skin by species of *Microsporum* and *Trichophyton.*

Clinical Characteristics. The early lesions of tinea circinata appear as flattened, reddish papules having a marked tendency to peripheral spread and central healing The margins of the lesion are sharply defined and scaly or vesicular. The infection may be accompanied by a varying degree of inflammatory response, or an eczematoid reaction as well as other variations (Fig V.10).

Diagnosis. Examination of potassium hydroxide preparations of scrapings from the lesions reveals the fungus etiology (see p 802) Cultures should be made for specific identification.

Treatment. In the presence of an acute inflammatory reaction initial treatment should consist of wet dressings of boric acid solution, Burow's solution diluted 1 20, aqueous solution of potassium perman-

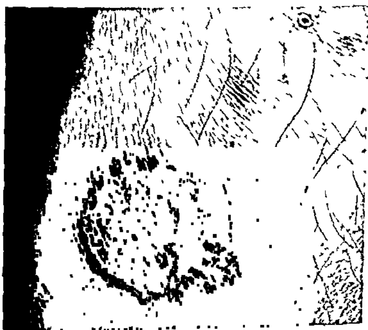


Figure V.10. Tinea circinata active vesicular border and scaling of center of lesion. (Courtesy Dr J Lamar Callaway Duke University)

ganate 1 5000 or calamine lotion When the acute process has subsided the following preparations are recommended

1 Whitfield's ointment one-half strength may be rubbed into the lesions two or three times daily

2 Five per cent ammoniated mercury ointment may be rubbed in two or three times daily or 3 per cent precipitated sulfur and 3 per cent salicylic acid in petrolatum should be rubbed in two or three times daily

3 One fourth to one half strength tincture of iodine may be painted on two or three times daily instead of No 2

4 If extensive the use of Griseofulvin should be considered

Tinea Imbricata

Synonyms Tokelau Burmese ringworm Malabar itch

Distribution Tinea imbricata is restricted to the tropics chiefly the islands of the South Pacific and the Malay Archipelago It also occurs *in southern China southern India Ceylon and central Africa It has* been reported from Colombia Brazil and Guatemala

Etiology It is due to infection of the skin by *Trichophyton concentricum*



Figure V 11 Tinea imbricata typical concentric scaling lesions on arm. (Courtesy of Dr N F Conant, Duke University Durham, North Carolina.)

Clinical Characteristics The early lesion of tinea imbricata appears as a raised brownish or reddish plaque which gradually extends peripherally. The superficial epithelium desquamates producing a scaling margin with the free inner edges of the scales turned up and directed toward the center of the lesion. Peripheral extension of the process leaves a smooth central area in which a new and similar lesion appears producing a further circle of scales within the peripheral circle. These scaled circles following one another may be one eighth to one half inch apart producing rosette like lesions (Fig V 11). There is no accompanying inflammatory reaction. The axillae groins face palms of the hands and soles of the feet are much less often affected than in the other cutaneous mycoses. The scalp is not involved. Itching is frequently intense.

Diagnosis The clinical appearance of the lesions is characteristic, and microscopic examination of a potassium hydroxide preparation of scrapings from the margin will reveal the mycelia of the fungus (see p 802). Cultures should be made and identified (see p 824).

Treatment 1 Chrysarobin ointment 5 to 10 per cent

2 Resorcinol 12 to 25 per cent in compound tincture of benzoin applied daily or twice daily to the lesions

3 Since extensive skin areas are usually involved the antibiotic Griseofulvin should be used

Tinea Versicolor

Synonym Pityriasis versicolor

Distribution This is a very common though unimportant mycotic infection of the skin

Etiology It is due to infection by *Malassezia furfur*

Clinical Characteristics Tinea versicolor is characterized by yellowish or brownish irregular macular patches which occur especially on the skin over the shoulders chest upper back axillae and upper abdomen. The individual lesions show fine scaling. Healing is frequently followed by partial depigmentation which may persist for a number of weeks or months (Fig V 12).

Diagnosis Potassium hydroxide preparations of scrapings from the lesion will reveal the characteristic clumping of round bodies and mycelial fragments

Treatment The following preparations are recommended

1 Fifteen per cent solution of sodium hyposulfite should be sponged on twice daily or

2 Pragmatar ointment may be applied to the lesions twice daily or

3 Three per cent sulfur and 3 per cent salicylic acid in petrolatum ointment may be applied each night

4 Daily baths with removal of all scales are necessary and are ren



Figure V 12 Tinea vers color brownish pigmented eruption. (Courtesy Dr J Lamar Callaway Duke University)

dered somewhat more efficacious by the use of vinegar which tends to loosen the scales

Otomycosis

Synonyms Singapore ear myringomycosis
Distribution It is common in the moist tropics and likewise is frequently observed in regions of high wind and dust
Etiology Many different saprophytic fungi have been isolated from this infection but the disease is primarily one of bacterial etiology
Clinical Characteristics. Otomycosis is a rare mycotic infection of the skin of the external auditory canal and may present variable clinical phenomena In mild cases the skin of the canal is reddened and

deeper structures are exceedingly rare Infection of the canal by bacteria may result in mild symptoms or in pustule formation cellulitis edema and occasionally intense pain (Fig V 13)
Diagnosis Microscopic examination of a potassium hydroxide preparation of scrapings from the lesion or of a portion of the mycelial mass reveals the mycelia and spores of *Candida* or the mycelia and



Figure V 13 Otomycosis (Courtesy Dr J Lamar Callaway Duke University)

so called fruit heads of *Aspergillus* or *Penicillium* The bacterial flora should be cultured and identified (p 824)

Treatment *If cellulitis with bacterial infection is present* the condition must be treated with compresses of saline or boric acid solution for one hour three times daily This should be followed by local application of chemotherapeutic agents selected by sensitivity tests against the cultured bacteria

If there is no bacterial infection as much of the mycelial mass cerumen and other debris as possible should be removed with a curette after thorough soaking with hydrogen peroxide After this one of the following regimens is recommended

1 The external canal is packed for 12 hours with a pledget of wool saturated with 1 per cent thymol in Cresatin The patient should be instructed to remove this if it produces severe burning Thereafter 1 per cent thymol in Cresatin drops are placed in the ear night and morning

2 Three per cent salicylic acid in 70 per cent alcohol may be swabbed in the external auditory canal and on the affected part of the ear twice daily

3 After the canal has been cleaned and dried with warm air it is packed for 12 hours with wool saturated with Cresatin Thereafter for eight days the canal is packed daily for nine minutes using a 1 per cent solution of thymol in alcohol For three days thereafter thymol iodide is dusted into the canal three times daily Concurrently the patient should take potassium iodide 1 8 grams by mouth daily for three days

4 After cleansing the canal with hydrogen peroxide solution it should be swabbed out with 12 per cent silver nitrate Alcohol drops should be introduced three times daily

5 Soap and water should be avoided locally, and the patient should not be allowed to go swimming

Prophylaxis. The prophylaxis of this infection is not satisfactory The use of plugs in the canal does not confer protection Precautions should be taken to keep the canal dry and protected against trauma with the finger or objects small enough to enter the canal

32

Systemic Mycoses

Unlike the dermatomycoses the systemic or deep mycotic infections are produced by members of many genera of the fungi, including representatives from the SCHIZOMYCETES, or true bacteria as well as

Table V.2. The Systemic Mycoses

DISEASE	ETIOLOGIC AGENTS
Actinomycosis	*Actinomyces bovis*
Maduromycosis	*Madurella mycetomi* *Madurella grisea* *Phialophora jeanselmei* *Allescheria boydii* (*Monosporium apiospermum*) *Cephalosporium falciforme*
Nocardiosis (= Mycetoma)	*Nocardia asteroides* *N brasiliensis* *N madurae* *N pelletieri* *N somaliensis*
Cryptococcosis	*Cryptococcus neoformans*
Candidiasis (= Moniliasis)	*Candida albicans*
Blastomycosis—North American	*Blastomyces dermatitidis*
Blastomycosis—South American	*B brasiliensis*
Coccidioidomycosis	*Coccidioides immitis*
Histoplasmosis	*Histoplasma capsulatum* *H duboisii* (Africa)
Sporotrichosis	*Sporotrichum schenckii*
Chromoblastomycosis	*Phialophora verrucosa* *Hormodendrum pedrosoi* *H compactum* *H carrionii*

Table V.3. Key to Microscopic Appearance of Pathogenic Fungi Found in Scrapings, Sputum, Pus, Etc

(*Does not apply to appearance in culture*)

1	(2)	Mycelia present	3
2	(1)	Without mycelia	7
3	(4)	Mycelia of bacterial narrowness	5
4	(3)	Mycelia broader than bacteria (yeastlike forms also present)	Moniliasis *Candida*
5	(6)	Mycelia like branching strings of bacteria	*Actinomyces*
6	(5)	Mycelia like long branching tubercle bacilli (some of them acid fast)	*Nocardia*
7	(8)	Yeastlike, budding forms	9
8	(7)	Saclike or sporelike, no budding	13
9	(10)	Within enormous gelatinous capsule	*Cryptococcus*
10	(9)	Without capsule	11
11	(12)	Thick double contoured wall, single buds	*Blastomyces dermatitidis*
12	(11)	Thick double-contoured wall multiple buds	*Blastomyces brasiliensis*
13	(14)	Extracellular, large	15
14	(13)	Usually intracellular, small	17
15	(16)	Sacs filled with endospores	*Coccidioides*
16	(15)	Spherical, dark brown spores showing equatorial splitting	*Phialophora, Hormodendrum*
17	(18)	Cigar-shaped, in polymorphonuclears (rarely seen)	*Sporotrichum*
18	(17)	*Like Leishman Donovan bodies, packed in WBCs*	*Histoplasma*

the FUNGI IMPERFECTI *Many tissues may be invaded, and the clinical* picture in consequence may be extremely variable Identification of the genera concerned may not be difficult, as is seen from Table V 3 Identification of species within the genera, however, may require specialized experience and training

An important feature of systemic mycotic infections is the common development of sensitization to the fungus and its products This reaction probably plays a significant part in the progress of the disease and likewise constitutes a factor of great importance in the planning of therapy Desensitization may prove an important adjunct to specific treatment with known chemotherapeutic agents Sensitivity should be evaluated by intracutaneous injection of a sterile extract of the fungus (for example, histoplasmin) or autogenous vaccines In the presence of a *positive skin test, desensitization should* be carried out by repeated graduated doses of vaccine The prognosis is bad in anergic patients who give negative skin tests in the presence of active infection, since this indicates that they have little or no resistance

Actinomycosis

Definition. A chronic, suppurating, granulomatous infection characterized by multiple abscesses and fistula formation, characteristic

granules of the fungus are present in the drainage from these lesions infection is produced by *Actinomyces bovis*

Distribution The causative organism is an obligate parasite of man and animals In humans it is found in the absence of disease on the mucous membranes of the mouth around carious teeth and in tonsillar crypts Because of this association the disease has a worldwide distribution

the anaerobic *Actinomyces bovis* and various species of aerobic *Nocardia* They are nonmotile gram positive in certain instances acid fast aerobic or microaerophilic organisms having branching threadlike mycelia seldom exceeding 1 μ in diameter In tissues sputum or pus *A bovis* is visible to the naked eye as the characteristic sulfur granule" composed of a mass of tangled branching mycelial threads which at the periphery of the granule may show radially arranged club shaped swellings giving rise to the term "ray fungus (Fig V 14)

Pathology The fundamental lesion is a granulomatous process in which the colonies of the fungus or granules of the *Actinomyces* are surrounded by mononuclear cells with occasional giant cells and numerous polymorphonuclear leukocytes in the areas of necrosis There is marked new connective tissue formation and fibrosis producing hard tumor like masses or indurations In these are multiple abscesses interconnected by sinus tracts often with multiple external fistula formations which discharge sanguinopurulent material containing the granules

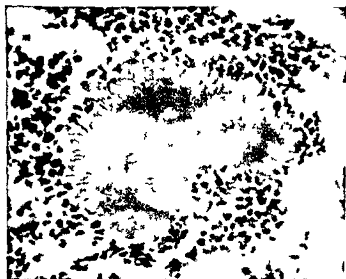


Figure V 14 Actinomycosis Sulfur granule in pus from sinus tract



Figure V 15 Actinomycosis of chest wall with draining sinuses Ribs involved and sinus tracts extending through abdominal wall. (Courtesy Dr D T Smith Duke University)

Extension of the infection is by continuity rarely by the blood stream or lymphatics (Fig V 15)

Clinical Characteristics The clinical types of actinomycosis fall into three general groups

1 Cervicofacial	50 per cent of cases
2 Abdominal	20 to 30 per cent of cases
3 Pulmonary	15 per cent of cases

In the *cervicofacial type* the portal of entry appears to be the mucous membrane of the mouth or pharynx Marked induration is produced and direct extension may lead to involvement of the bones of the skull or to the skin with the formation of multiple fistulous tracts Pain is not marked and there may be little or no systemic reaction

The *abdominal or intestinal type* usually originates in the region of the appendix and cecum with the formation of a gradually increasing mass in the right lower quadrant followed by internal and external sinus formation Extension occurs to adjacent structures often with involvement of the liver and spleen and subsequently the lung Abdominal actinomycosis may be accompanied by toxemia fever chills and other evidence of an intra abdominal inflammatory process

The *pulmonary type* may be primary or secondary to a cervicofacial lesion with extension through the mediastinum It is characterized by cough sputum hemoptysis fever dyspnea and night sweats Invasion of the pleura is accompanied by pain and empyema is not unusual This is frequently followed by invasion of the chest wall with the development of areas of induration abscess formation and multiple external

sinuses Involvement of the mediastinum may be followed by invasion of the esophagus or pericardium

Diagnosis. The combination of the clinical picture and demonstration of the characteristic sulfur granules in the tissues, or in pus, is characteristic Microscopic examination of a granule crushed beneath a coverglass revealing the characteristic structure and the presence of branching mycelial threads, permit specific diagnosis of infection by a member of the family ACTINOMYCETACEAE The material should be cultured on suitable media under both anaerobic and aerobic conditions

Treatment Penicillin, Aureomycin and chloramphenicol (Chloromycetin) have been used successfully Penicillin however is the drug of choice Associated organisms may necessitate concurrent treatment with sulfonamides and/or streptomycin

Maduromycosis

Synonym. Madura foot

Definition. The term madura foot is used to define a clinical entity characterized by a chronic granulomatous process usually limited to the lower extremities, producing extensive destruction of the soft tissues and the bony structures particularly of the feet It is caused by many different filamentous fungi

Distribution. Maduromycosis is widespread in India especially in the Madras Presidency and in Africa Ceylon Cochin China Indonesia and Madagascar Sporadic cases have been reported from Italy Greece the West Indies Cuba Argentina and occasionally the United States

Etiology. The disease is produced by several different fungi *Allescheria boydii*, *Cephalosporium falciforme* and others (see p 231)

Pathology. There is extensive invasion by the fungus The early lesion is granulomatous in character with the fungus granules or colonies in edematous granulation tissue infiltrated with mononuclear cells and polymorphonuclear leukocytes As the lesion progresses it is surrounded by a dense fibrous capsule and often intersected by fibrous trabeculae There is extensive necrosis of tissue and thrombosis of vessels In advanced cases the foot becomes a mass of cystlike areas with intercommunicating sinus tracts and multiple externally draining sinuses In these instances there is complete destruction of muscles, bones and tendons (Fig V 16)

Clinical Characteristics The initial lesion usually appears on the sole of the foot as a superficial or deep cutaneous nodule The overlying skin becomes discolored and breaks down, and a persistent sinus tract develops In other instances the process may begin as a deep abscess ultimately opening externally As extension occurs, the foot becomes enlarged, presenting a convex sole and swollen dorsum Nodules appear



Figure V 16 Madura foot.



Figure V 17 Mossy foot a superficial verrucous dermatitis of varied bacterial etiology (Alan Fisher for the Office of the Coordinator of Inter American Affairs)

in uninvolved areas of the skin breaking down to form new sinuses Ultimately the foot may be enlarged to three or four times the normal size

There is little or no systemic reaction and in uncomplicated cases little or no lymphangitis or lymphadenitis

Diagnosis. The clinical picture, together with demonstration of the characteristic granules composed of wide, septate branching mycelia and the development of a typical mold in culture, is diagnostic Mossy foot should not be confused with this condition (Fig V 17)

Treatment. Early diagnosis may allow successful treatment by surgical intervention penicillin and sulfonamides The in vitro activity of nystatin and diaminodiphenylamine dihydrochloride against some of the fungi causing madura foot should warrant their use in selective cases

Nocardiosis

Synonyms Actinomycotic mycetoma systemic nocardiosis

Definition A subacute or chronic infection of the subcutaneous tissues characterized by tumor like lesions often discharging through with protean symp meningitis or brain

Distribution The causative organisms are widely distributed in nature, therefore, there is no particular geographic distribution of the disease although certain clinical types are encountered more frequently in the tropics

Etiology. Species of *Nocardia* are aerobic members of the ACTINOMYCETACEAE which have gram positive branching threadlike mycelia 1 μ in diameter One species, *N asteroides* is also acid fast. In tissue and from draining sinuses in mycetoma the fungus may be organized into granules with or without clubs which cannot be distinguished micro-



Figure V 18 Nocardiosis actinomycotic mycetoma caused by *Nocardia asteroides.* (Courtesy Dr Norman F Conant Duke University)



Figure V 19 Nocardiosis pulmonary nocardiosis caused by *Nocardia asteroides* (Courtesy Dr Norman F Conant, Duke University)

Pathology. In subcutaneous tissues multiple abscess formation with resulting chronic inflammatory response leads to granulomatous processes with large cell infiltration, giant cells and fibrosis The organism is usually seen in the areas of necrosis as granules of varying size Systemic nocardiosis is the result of hematogenous spread from a primary pulmonary infection, resulting in generalized pyemia with abscesses and granulomatous lesions found in many organs

Clinical Characteristics Subcutaneous tissues are inoculated with the organism by trauma to establish a slowly evolving chronic suppurative disease characterized by swelling and multiple fistulae Spread through tissue by contiguity, with fibrosis, and bone destruction and tumefaction result in a mycetoma (Fig V 18)

Systemic infection follows a primary pulmonary disease which may simulate tuberculosis or a malignant neoplasm Hematogenous spread resulting in abscess formation in many organs including the brain causes protean symptoms which makes a differential diagnosis difficult (Fig V 19)

Diagnosis The clinical picture of mycetoma is identical with that of subcutaneous infe
caused by a variety c
whole and crushed g
either may be seen
up into branching, gram positive bacillary elements 1 μ in diameter Differentiation by cultures is essential *A bovis* is anaerobic, whereas

Nocardia species grow well aerobically on Sabouraud's glucose medium at room or incubator temperatures. The granules of actinomycetic mycetoma and those of maduromycosis may be distinguished microscopically or by culture. Microscopically the granules of *Nocardia* are composed of delicate hyphae 1 μ in diameter, whereas those of the filamentous fungi are composed of wide septate hyphae 2 to 2.5 μ in diameter. In culture *Nocardia* species appear similar to cultures of saprophytic acid-fast organisms, whereas the filamentous fungi develop as typical molds.

Treatment The sulfonamides offer specific therapy for infections caused by *Nocardia*. Treatment with sulfadiazine alone, or in combination with sulfamerazine to obtain higher serum concentrations, has proved effective.

Cryptococcosis

Synonyms European blastomycosis, Busse-Buschke's disease, torula meningitis.

Definition A subacute or chronic infection by a yeastlike fungus (*Cryptococcus neoformans*) which has a predilection for invasion of the central nervous system. Two clinical types are recognized: the *cutaneous form*, characterized by acneform lesions and subcutaneous nodules, may precede or follow the *generalized form*, in which a primary pulmonary infection is followed by invasion of the body, especially the central nervous system.

Distribution The fungus is widely distributed in nature and has been isolated from the soil, plants and animals. Human infections have been reported from Europe, India, Australia, Japan, Canada, the United States, and Central and South America.

growth with the budding cells exhibiting the characteristic capsule.

Pathology The cutaneous form may produce acneform lesions, granulomatous ulcers and deep nodules or tumor-like masses which are filled with gelatinous material. There is commonly little acute inflammatory reaction, but there is infiltration with giant cells, "foam" cells, plasma cells and lymphocytes together with fibroblasts and newly formed connective tissue. At times typical tubercles are produced.

In the central nervous system a variety of pathologic changes may be seen, including diffuse meningitis, granulomas in the meninges, endarteritis, infarcts, areas of softening, increase in neuroglia, and extensive destruction of nerve tissue (Fig. V 20).

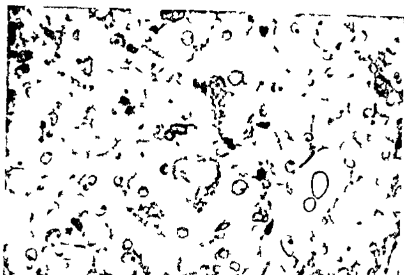


Figure V 20 Cryptococcosis Torula meningitis H & E stain showing numerous organisms

The organisms are present singly or in groups in the lesions

Clinical Characteristics The *cutaneous type* (European blastomycosis) may precede or follow *systemic infection It is characterized by* pustule formation granulomatous ulcers of the skin or subcutaneous tumors

The *generalized type* (torula meningitis) is usually characterized by symptoms and signs of extensive and progressive involvement of the central nervous system In this form the onset is usually insidious although occasionally sudden with fever headache and vomiting Death usually occurs after the onset of coma with signs of increased intracranial pressure *The spinal fluid is usually under increased pressure and* the cell count increased to 200 to 800 per cubic millimeter the cells are chiefly mononuclear The organisms may be present in small numbers and may be mistaken for erythrocytes or small lymphocytes This form of the disease is often mistaken for tuberculous meningitis

Involvement of the lungs is accompanied by cough and signs of chronic bronchitis with peribronchial involvement which may be confused with pulmonary tuberculosis A low grade intermittent fever may be present

Rarely invasion of the liver spleen and joints occurs among the latter the knees are most commonly affected

The prognosis is grave in both the cutaneous and generalized forms and untreated central nervous system infections are invariably fatal

Diagnosis The fungi appear in infected tissue spinal fluid, *sputum or the gelatinous content of subcutaneous* nodules as characteristic round or ovoid single budding yeastlike bodies with heavy capsules Satisfactory demonstration of the capsule requires smears in India ink of the sediment from centrifuged spinal fluid or *of pus* (Fig V 21)

Treatment Local and multiple cutaneous lesions as well as pulmonary and bone lesions often respond to extensive sulfonamide ther

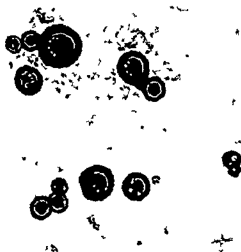


Figure V.21 *Cryptococcus neoformans* in pus (Courtesy Dr Donald S Martin Communicable Disease Center USPHS)

apy However these drugs are fungistatic and after varying periods recurrence with meningitis may occur Amphotericin B is considered to offer specific therapy for all forms of cryptococcosis

Candidiasis

Definition An infection by a yeastlike fungus *Candida albicans* which occasionally involves the skin and deeper tissues particularly the

the lesions with occasional mycelia On Sabouraud's medium white yeastlike colonies that have a yeasty odor are formed

Clinical Characteristics *Candida albicans* has frequently been recovered from the normal mouth throat and gastrointestinal tract It is commonly present in the sputum of patients with pulmonary tuberculosis or carcinoma of the lung It is likewise frequently present in the stools of patients with pernicious anemia sprue and various other gastrointestinal diseases It is usually difficult to ascribe definite etiologic significance to the presence of this fungus

Candida albicans has been shown to be capable occasionally of producing a primary bronchitis infections of the skin and systemic infec-

tions The most common conditions attributed to it are thrush onychia paronychia and dermatitis in moist skin areas particularly the axillae beneath the breasts and in the intergluteal folds The rare systemic infections which are highly fatal include abscess formation and meningitis

Secondary infection with *C albicans* may follow extensive therapy with wide spectrum antibiotics (tetracyclines) During prolonged treatment with such drugs therefore the patient must be observed constantly to avoid secondary infections which may prove serious

Diagnosis The ubiquity of this fungus necessitates extreme caution in etiologic diagnosis Examination of scrapings from the skin or nails or of sputum or other material in 10 per cent potassium hydroxide preparations demonstrates the round single or budding yeast forms and occasionally mycelia The appearance in culture and the lesions produced in the kidneys after intravenous injection into rabbits are characteristic (see p 824)

Treatment. Cutaneous infections by *C albicans* may be treated as follows

1 Soaking twice daily for 30 minutes with 1 1500 potassium permanganate solution

2 Daily application of 1 per cent solution of gentian violet

Oral lesions should be treated with alkaline mouthwashes or by irrigations with gentian violet 1 10 000 Nystatin solutions may be used as a mouthwash and should be retained in the mouth for a few minutes before swallowing For vaginitis douches of potassium permanganate 1 1500 or gentian violet 1 10 000 also propionate and nystatin vaginal jelly are recommended

The pulmonary are the more important of the systemic infections Nystatin by mouth or Amphotericin B intravenously should be used in such infections To avoid complicating secondary infections by species of *Candida* Mysteclin a combination of nystatin and a tetracycline should be used

Blastomycosis

Synonyms (1) North American blastomycosis Gilchrist s disease (2) South American blastomycosis Lutz Splendore Almeida s disease

North American Blastomycosis

Definition An infection due to *Blastomyces dermatitidis* The cutaneous type is characterized by granulomatous ulcerating lesions the systemic type by a close resemblance to tuberculosis with involvement of the lungs and less often the abdominal viscera the skeletal system and the central nervous system

Distribution. North American blastomycosis is recognized at present only in the United States and Canada

Etiology. *Blastomyces dermatitidis* appears in tissue and pus as single, budding, round or ovoid yeastlike cells 8 to 15 μ in diameter



Figure V 22 *Blastomyces dermatitidis* Budding yeastlike cells in tissue section.

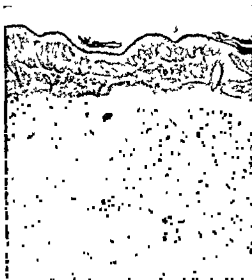


Figure V.23 North American blastomycosis Granulomatous lesion in subcutaneous tissues.



Figure V 24 North American blastomycosis (Courtesy Dr J Lamar Calloway Duke University)



Figure V 25 North American blastomycosis (Courtesy Dr J Lamar Calloway Duke University)

They have a thick refractile outer wall often giving a double-contoured appearance Mycelia are not present (Fig X 22)

Growth in culture at 37° C is yeastlike and at room temperature moldlike with cottony growth of branched aerial mycelia

Pathology The rare primary cutaneous lesion usually appears on an exposed skin surface developing into a verrucous peripherally extending crater like ulcer with raised irregular undermined edges and a granulation tissue base The visceral type closely simulates tuberculosis but numerous small abscesses with polymorphonuclear leukocytic infiltration are produced (Fig X 23)

Clinical Characteristics. The cutaneous lesions of North American blastomycosis usually occur on the face neck hands wrists arms feet or legs appearing first as papules or pustules and extending to form the chronic ulcers There is usually little pain tenderness or systemic reaction and commonly no lymphadenitis (Figs X 24 X 25) Such lesions evolve as metastases to the subcutaneous tissues from an established systemic infection Primary cutaneous infection by direct inoculation is characterized by a lymphadenitis

Systemic infections usually start in the lungs frequently producing a clinical picture that is confused with tuberculosis or malignant neoplasms

Diagnosis The characteristic budding organisms are found within giant cells in granulation tissue and in necrotic material from the lesion They may be demonstrated in the sputum in cases of pulmonary infection

Treatment. The prognosis is unfavorable in mergic patients who give negative skin tests in the presence of active infection since the negative skin test indicates that the patient has little or no resistance Also the complement fixation titer indicates the extent of disease the higher the titer the more widespread the infection

Stilbamidine dihydroxystilbamidine and or Amphotericin B can be used for specific treatment of North American Blastomycosis These drugs are toxic however and the patient should be closely watched for signs that may contraindicate their continued use

South American Blastomycosis

Definition. An infection by *B brasiliensis* which has a predilection for lymphatic tissue The disease appears in two forms a cutaneous type usually starting about the mouth and a lymphaticovisceral type with involvement of the lymphatics liver and spleen There may be secondary pulmonary involvement primary pulmonary infection may also occur

Distribution South America principally Brazil

Etiology *Blastomyces brasiliensis* (*Paracoccidioides brasiliensis*) appear in the lesions as thick walled round or ovoid yeast cells resembling *B dermatitidis* except that they are characteristically larger reaching diameters of 60 μ Multiple budding forms are likewise characteristic

Clinical Characteristics. The portal of entry is usually the buccal cavity A slowly extending ulcer is produced This has a granular base



Figure V 26 South American blastomycosis Metastatic lesion in liver showing many round and ovoid forms of *B brasiliensis*

presenting numerous pinpoint yellowish white areas in which the fungus is particularly abundant The infection may extend to adjacent skin areas producing lesions similar to those of the North American disease The primary lesion may extend directly to the tonsils and secondarily to lymphoid follicles in the gastrointestinal tract producing nodules and follicular ulceration This may be followed by involvement of the regional lymphatics and invasion of the spleen and the liver (Fig V 26)

Diagnosis Diagnosis is based upon demonstration of the large multiple budding yeastlike forms

Treatment The sulfonamides are specific for this disease Also Amphotericin B has been said to be curative

Coccidioidomycosis

Synonyms Coccidioidal granuloma San Joaquin fever valley fever

Definition An acute subacute or chronic infection of the lungs produced by *Coccidioides immitis* acquired by inhalation Clinically it resembles acute bronchitis or pulmonary tuberculosis Occasionally there is involvement of the skin bones joints lymph nodes larynx meninges

and other visceral structures as a result of metastases from the primary pulmonary infection Multiple cold abscesses are not uncommon

Distribution. The disease is endemic in the southwestern United States and sporadic cases have been reported from the Hawaiian Islands Italy and southeastern Europe Many cases which have been reported from Brazil have been confused with paracoccidioides infections (*B brasiliensis*)

Etiology *Coccidioides immitis* appears in tissue and exudates as round non budding, thick walled spherules measuring 20 to 80 μ in diameter and containing numerous endospores Culture on Sabouraud's medium at room temperature produces a cottony white growth becoming brownish in color with branching septate filamentous hyphae which subsequently break up with the formation of arthrospores

Epidemiology *Coccidioides immitis* has been recovered from the soil and from pulmonary lesions in various wild rodents in the endemic areas in the southwestern United States and it has been suggested that it is primarily a rodent disease It has also been reported to produce infection in cattle sheep and dogs Infection of man occurs by inhalation of dust containing the highly infectious chlamydospores There is no evidence of direct animal to man or man to man transmission Primary infections have a definite seasonal incidence occurring predominantly in the hot dusty autumn months

Pathology The fundamental pathology is that of a granulomatous process acute subacute or chronic in nature accompanied by varying degrees of fibrosis with or without central necrosis of the lesion (Fig V 27)



Figure V.27 Coccidiodes immitis Round immature spherules and endospore filled spherule in section of lung Courtesy Dr Norman F Conant Duke University)

In chronic lesions of the lung cavity formation or pleurisy with effusion may occur The organisms are surrounded by giant cells epithelioid cells lymphocytes and plasma cells

Occasional granulomatous masses may reach considerable size without necrosis Abscess formation however is more frequent than in tuberculosis

Clinical Characteristics Primary pulmonary infection produces the clinical picture of pneumonia or acute bronchitis with or without sputum and is occasionally accompanied by pleurisy with effusion Physical signs may be absent In the majority of cases recovery occurs in two to three weeks without sequelae Sensitivity to the organism frequently develops and may be manifested by erythema multiforme or *erythema nodosum* This form of the disease is known as "San Joaquin fever or valley fever These infections are accompanied by an initial leukocytosis with a normal differential count Later there is lymphocytosis with an increase in large mononuclear cells and eosinophilia

The secondary or chronic phase of the disease coccidioidal granuloma develops by dissemination of the infection from the primary focus either in the course of the acute attack or subsequently Lesions may occur anywhere in the body producing a variety of signs and symptoms

Diagnosis Diagnosis is based upon demonstration of the large non budding thick walled spherules containing numerous endospores in clinical materials and the development of a cottony culture with typical arthrospores on Sabourauds glucose agar Intratesticular injection of infected material into guinea pigs produces lesions containing the typical endospore filled spherules

A positive skin test to coccidioidin has the same significance as the tuberculin test in tuberculosis

Precipitins are present in primary cases and complement fixing antibodies increase in titer as the disease progresses

Differential diagnosis entails differentiation from tuberculosis syphilis bacterial osteomyelitis malignant neoplasms and other mycotic infections

Treatment Most primary infections heal without specific treatment There is no specific treatment for progressive coccidioidomycosis unless Amphotericin B proves effective

Histoplasmosis

Definition A self limited primary pulmonary infection caused by *Histoplasma capsulatum* which heals by calcification or a progressive systemic disease of the reticuloendothelial system

Distribution The majority of reported cases have been from the Mississippi and Ohio valleys and the Appalachian mountains in the

United States There are isolated reports of cases from the Panama Canal Zone Philippine Islands Honduras Argentina Brazil, Java, Japan and England A disease referred to as African histoplasmosis differs from the classic type in the appearance of large yeast forms of the fungus, *H duboisii*, in the tissues

Etiology. *Histoplasma capsulatum* appears as a small encapsulated organism 1 to 5 μ in diameter in mononuclear cells in the blood and in the reticuloendothelial cells of the internal organs and bone marrow

Cultivation on blood agar at 37° C produces a yeastlike growth of small oval budding cells On Sabouraud's medium at room temperature growth is moldlike at first cottony and white later becoming brown

Epidemiology *Histoplasma capsulatum* has been isolated from the soil and from numerous animals Infection in man probably occurs by inhalation There is no evidence of animal to man transmission

Pathology Systemic histoplasmosis is a disease essentially of the reticuloendothelial system Grayish or white nodules or more or less extensive areas of necrosis surrounded by granulomatous tissue are produced The organisms multiply in the reticuloendothelial cells and may be seen in phagocytic cells in the lesions (Fig V 28)

Clinical Characteristics Primary pulmonary infection may be asymptomatic or simulate a mild cold bronchitis influenza or tuberculosis Such an infection results in sensitivity to histoplasmin and spontaneous recovery usually results in miliary calcification which may be detected months or years later by routine x ray In many areas of the United States large population groups have been found to have non tuberculous pulmonary calcifications with a positive histoplasmin skin



Figure V 28 *Histoplasma* in Kupffer cell of liver (Courtesy Dr Norman F Conant, Duke University)

test and a negative tuberculin skin test. Such individuals are thought to have had primary histoplasmosis as described above.

Systemic progressive infection may result in nasopharyngeal ulcerations resembling carcinoma, pulmonary infection with diffuse or localized consolidation, abscess or cavitation resembling tuberculosis or visceral infection resembling leishmaniasis. Not infrequently lymphadenopathy suggests lymphosarcoma, Hodgkin's disease or leukemia.

Diagnosis The organisms stain well with Wright's stain and in infected cells may be confused with Leishman-Donovan bodies or *Toxoplasma*. They may be demonstrated in blood films or in smears of the sternal marrow or splenic pulp. Final identification is based on cultures which demonstrate typical colonies and tuberculate spores of *H. capsulatum*.

Treatment Amphotericin B provides prompt and complete clinical response in acute disseminated histoplasmosis with resulting remission for several years in some cases. In chronic progressive histoplasmosis Amphotericin B therapy is associated with resolution of lesions and clinical improvement; however, organisms may persist in areas of cavitation or caseation.

Sporotrichosis

nfection
ilcers
odes

Distribution Worldwide.

Etiology. Sporotrichosis is produced by infection with *S. schenckii* which is widely distributed in nature. In infected experimental animals this organism produces gram-positive, cigar-shaped spores which are readily seen in polymorphonuclear leukocytes. They are rarely seen in man.

Pathology The gumma-like nodules usually show a central necrotic area surrounded by granulation tissue, epithelioid cells and giant cells with a peripheral zone of connective tissue.

Clinical Characteristics The initial lesion usually appears as a hard, movable, elastic nodule beneath the skin. This enlarges and becomes attached to the skin, which becomes red, inflamed and then necrotic with the formation of a chronic ulcer. Similar nodules develop along the superficial lymphatics draining the area, resulting in the formation of secondary ulcers. The lymphatic channels between the lesions are frequently palpable, thickened and cordlike (Fig. V-29).

Rarely other structures, including mucous membranes, muscles, the skeletal system and the viscera, may be involved.

When untreated the lesions may persist for years.



Figure V 29 Sporotrichosis showing active and healed lesions (Courtesy Dr J Lamar Callaway Duke University)

Diagnosis *Sporotrichum schenckii* is rarely demonstrable in material from the lesions in man Diagnosis is based upon the cultural characteristics after inoculation of infected material on Sabouraud's medium (see p 824) and inoculation into laboratory animals—rats mice or guinea pigs

Treatment. Potassium iodide is a specific for this infection and should be administered from the outset in massive dosage

Chromoblastomycosis

Definition A fungus infection of the skin producing verrucous wartlike nodules or papillomata which may or may not ulcerate

Distribution This disease occurs sporadically in many areas of the world

Etiology Chromoblastomycosis is produced by a variety of fungi—*Phialophora verrucosa Hormodendrum pedrosoi H compactum* or *H carrionii* All of these present an identical appearance in pus or in sections of tissue from the lesions They appear as clusters of large spherical dark brown spores which reproduce by equatorial splitting and not by budding Specific identification is based upon the characteristics in culture on Sabouraud's medium at room temperature

Pathology. The pathology is essentially that of an infectious granuloma with numerous giant cells mononuclears phagocytes epithelioid cells and plasma cells The organisms may be seen lying free within dermal abscesses or within giant cells

Clinical Characteristics Chromoblastomycosis is a very chronic infection usually occurring on the extremities It appears first as pustules which subsequently develop into elevated scaling warty nodules or papillomata the *infected extremities gradually* become covered with these lesions When infection occurs on the face neck or buttocks the lesions are often atypical

Diagnosis Diagnosis is based upon demonstration of the characteristic spores in smears of exudate or in potassium hydroxide preparations of scrapings from the lesions

Treatment When the infection is superficial and not too extensive surgical excision is recommended Iodides have no effect Iontophoresis with copper sulfate is said to be useful

VI

Protozoal Diseases

33

The Intestinal Protozoa

Infection of the human intestine by certain members of the Protozoa is common in many parts of the world. Several species of amebae

Table VI 1. Some Important Intestinal Protozoa of Man

ORGANISM	POTENTIAL PATHOGEN	ALWAYS NON PATHOGENIC	STAGES OF ORGANISM	
			TROPHOZOITE	CYST
Amebae				
Entamoeba histolytica[1]	+	−	+	+
E coli	−	+	+	+
Iodamoeba butschlii		+	+	+
Endolimax nana	−	+	+	+
Dientamoeba fragilis	?		+	−
Flagellates				
Chilomastix mesnili	−	+	+	+
Trichomonas hominis	−	+	+	−
T vaginalis	+	−	+	−
Giardia lamblia	+		+	+
Retortamonas intestinalis	−	+	+	+
Enteromonas hominis		+	+	+
Ciliate				
Balantidium coli	+	−	+	+
Sporozoa				
Isospora hominis	+		•	•
Isospora belli	+	−	•	•

[1] For E. hartmanni see p 260

* See pp 268 269 for stages of intestinal sporozoa

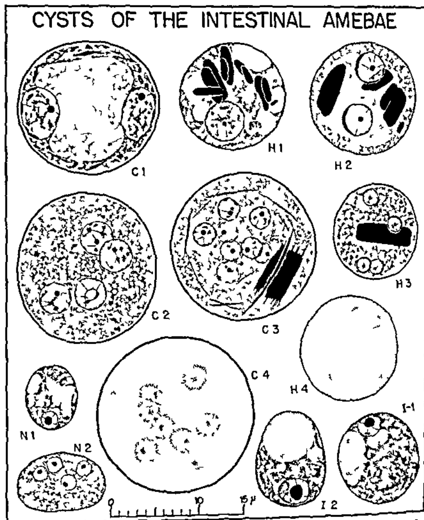


Figure VI 1 C-1 Iron hematoxylin stained binucleate cyst of *Entamoeba coli* C-2 Iron hematoxylin stained quadrinucleate cyst of *E coli* C-3 Iron hematoxylin stained mature cyst of *E coli* H 1 Iron hematoxylin stained uninucleate cyst of *E histolytica* H 2 Iron hematoxylin stained binucleate cyst of *E histolytica* H 3 Iron hematoxylin stained mature cyst of *E histolytica* N 1 Iron hematoxylin stained uninucleate cyst of Endolimax *nana* N 2 Iron hematoxylin stained mature cysts of *E nana* I 1 I 2 Iron hematoxylin stained mature cysts of *Iodamoeba butschlii* C-4 Unstained mature cyst of E coli H 4 Unstained cyst of *E histolytica*

flagellates sporozoa and a ciliate which are of medical importance may be encountered Of these the ameba *Entamoeba histolytica* and the ... for man The ameba ... and the sporozoa ... tomatic infections ... 1900)

The remaining organisms are of importance partly because of diagnostic problems which they may present and partly for the evidence they

furnish us to the environment in which their host has previously lived Those organisms whose modes of transmission are known are spread from one individual to another by contamination of food or drink with human feces In the case of *B coli* it is probable that infection of man

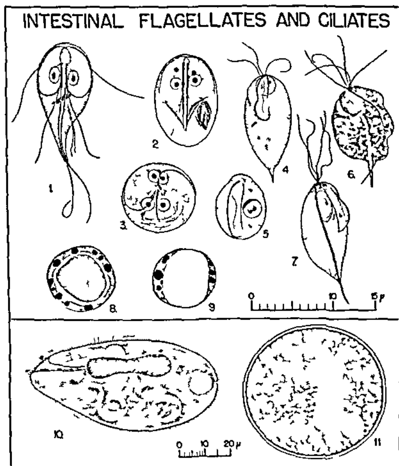


Figure VI.2. 1 Iron-hematoxylin stained trophozoite of *Giardia lamblia* 2 Iron hematoxylin stained cyst of *G lamblia* 3 Iron hematoxylin stained cyst of *G lamblia* end view 4 Iron hematoxylin stained trophozoite of *Chilomastix mesnili* 5 Iron hematoxylin stained cyst of *C mesnili* 6 Iron hematoxylin stained trophozoite of *Trichomonas hominis*. 7 Iron hematoxylin stained trophozoite of *T vaginalis* 8 Iron hematoxylin stained *Blastocystis hominis*. 9 Unstained *B hominis*. 10 Trophozoite of *Balantidium coli*. 11 Unstained cyst of *B coli*.

Table VI.2. Salient Features of Viable Trophozoites of Some Intestinal Protozoa of Man

PARASITE	SIZE (μ) LIVING	NORMAL MOTILITY	PSEUDOPODIA	STAINED NUCLEUS	OTHER CHARACTERISTICS
Entamoeba histolytica	10–25 (Rounded forms)	Active, progressive, streaming, cytoplasm flows into pseudopod	Tonguelike, explosively formed	Round, minute karyosome, fine chromatic lining of membrane, ringlike	Living nucleus not visible
E coli	20–30 (Rounded forms)	Sluggish, not progressive	Blunt, hemispheric, semilunar	Round, coarse karyosome, coarse chromatic lining of membrane, ringlike	Living nucleus visible
Iodamoeba butschlii	9–13 (Rounded forms)	Like *E coli*	Like *E coli*	Round, large round karyosome	
Endolimax nana	8–12 (Rounded forms)	Usually nonmotile, occasionally slightly progressive	Round, budlike	Round, large, irregular karysome	
Dientamoeba fragilis	5–20 (Rounded froms)	Usually sluggish or nonmotile	Triangular (tentlike), rectangular, veil like, cloverleaf	2 (or 1) nuclei, with mass of chromatin granules embedded in clear matrix	
Chilomastix mesnili	13–24 × 6–11	Flagellate, spiral, body rigid	———	Round, small eccentric or central karyosome	Body pear-shaped, buccal structures prominent, spiral twist in body

Trichomonas hominis	10 15 × 5 8	Flagellate continuous jerky wobbly body plastic	Round or oval karyosome more or less central	3 5 anterior flagella, undulating membrane and axostyle present
T. vaginalis	10 30 × 5 15	Similar to *T. hominis*	Elongate oval chromatin grains small and uniformly distributed	4 anterior flagella, undulating membrane short
Giardia lamblia	11 18 × 6 9	Active tumbling and turning like falling leaves spinning	Right and left nuclei ovoid with prominent irregular karyosomes	Has sucking disk 8 flagella
Retortamonas intestinalis	4 [illegible] × 3 4	Flagellate jerky and progressive	Round membrane delicate karyosome eccentric	2 anterior flagella and 2 blepharoplasts near nucleus
Enteromonas hominis	4 10 × 3 6	Similar to *R. intestinalis*	Ovoid membrane delicate karyosome large	Body pear shaped 3 anterior flagella and 1 along flattened surface and extending free posteriorly
Balantidium coli	50 70 × 30 60	Ciliate strong progressive swimmer rapid gliding	Macronucleus sausage shaped micronucleus ovoid or round	V shaped peristome anus at posterior end
—	—		—	

Table VI 3 Salient Features of Cysts of Some Intestinal Protozoa of Man

PARASITE	USUAL SHAPE	USUAL SIZE (µ)	NUMBER NUCLEI	NUCLEAR KARYOSOME	GLYCOGEN MASS (IN IODINE)	CHROMATOID BODIES	OTHER CHARACTERISTICS
Entamoeba histolytica	Round	6-15	1-4	Small granule	Diffuse brown in young cysts	Rod-shaped or thick bars	In fresh unstained cyst, *nuclei not visible*; chromatoids conspicuous when present
E. coli	Round	15-20	1-8	Coarser than in *E. histolytica*	Large, deep brown in young cysts	Splinter-like or filamentous	Nuclei usually visible in unstained cyst; cyst *wall heavy*
Iodamoeba bütschlii	Ovoid Round	6-15	1-2	Bulky, round	Large or small, sharply delimited, *deep brown*	None	Usually granular mass next to karyosome
Endolimax nana	Ovoid Round	7-10 × 6-7	1-4	Eccentric mass	Occasionally present in *young cysts*	None	Often cytoplasmic volutin granules confused with karyosomes
Chilomastix mesnili	Lemon-*shaped*	7-9 × 4.5-6	1	Mass at one pole	Sometimes present	None	*Oral apparatus beside nucleus*
Giardia lamblia	Ovoid	8-12 × 6-10	4	Punctiform, central	None	None	Nuclei at anterior pole; fibrils in cytoplasm
Retortamonas intestinalis	Pear-shaped	4-7 × 3-5	1	Slightly eccentric	None	None	Cyst wall appears *double in fresh preparation*; margin of cytosome may show *when stained*
Enteromonas hominis	Elongate Ovoid	6-8 × 4-6	1-4	Small, central	None	None	1 or 2 nuclei at each end; well-defined cyst wall
Balantidium coli	Round	50-65	1 macronucleus 1 *micronucleus*	—	None	None	Macronucleus kidney-shaped; large contractile vacuole present
Isospora hominis	Ovoid	Sporocyst 10 × 15	—	—	None	None	Oocyst wall usually absent; sporocysts single or paired
I. belli	Ovoid	Oocyst 12 × 30	—	—	None	None	Oocyst wall present; 2 sporocysts 9 × 11 µ each within oocyst wall
Blastocystis hominis (A yeast, *not a protozoan*)	Round	10-15	1-8	—	None	None	Nuclei marginal between inner and outer wall

because of its common occurrence in stools and the frequency with which it may be confused with encysted forms of certain of the intestinal protozoa

Most of the intestinal protozoa of man pass through two stages an active trophozoite stage and a resting nonmotile or encysted stage The trophozoites are motile they feed actively and undergo multiplication by binary fission Subsequently certain of the trophozoites cease feeding lose their motility and secrete a cyst wall These encysted forms or cysts are much less susceptible to changes of environment than are the trophozoites and they are primarily responsible for transmission of the infection (Table VI 1) Trophozoites do not long survive in nature outside the favorable environment of the intestinal tract

Identification of the individual protozoan is based upon certain specific characteristics of the trophozoite and of the cyst These distinguishing features include the type of motility of the trophozoite food inclusions the number and structure of the nuclei and other morphologic details Similarly the encysted forms may be distinguished by differences in size and shape by the number and structure of the nuclei the characteristics of chromatoid bodies when these are present the amount and distribution of contained glycogen and by other details of the internal morphology (Figs VI 1 VI 2 VI 4 VI 5) To demonstrate all of these features it is frequently necessary to examine not only unstained fresh preparations but also films stained by iodine and fixed smears stained by Heidenhain's or other iron hematoxylin methods The latter techniques are essential for demonstration of the finer morphologic details upon which specific identification is based These methods are described on pages 803 813

Certain of the intestinal protozoa may be isolated and maintained in artificial culture media

The important differential features of the trophozoites and the cysts are indicated in Tables VI 2 VI 3 and VI 4

Entamoeba histolytica

Entamoeba histolytica Schaudinn 1903 is an important pathogenic parasite of man It localizes principally in the colon and only rarely invades the terminal ileum Metastatic lesions particularly of the liver may follow invasion of the blood stream The life cycle includes both trophozoite and encysted stages

The Trophozoite Iron hematoxylin stained specimens are usually 15 to 25 μ in diameter There is a single spherical nucleus with a delicate nuclear membrane the inner surface of which is lightly encrusted with a layer of minute chromatin granules Within the nucleus there is a small punctiform karyosome Ingested erythrocytes may be present in the cytoplasm

The living unstained organism exhibits active progressive motility which is characteristic of this species The ameba usually assumes a ribbon like form and moves across the microscope field by continuous flowing of cytoplasm into the leading element This "anterior" portion or pseudopod of ectoplasm is clear and glasslike often contrasting

sharply with the less hyaline or finely granular endoplasm of the ameba The nucleus is usually not visible Motility is rapidly lost as the trophozoite is cooled below the temperature of the human body, at which time the distinction between the glasslike *pseudopodia and the more* granular endoplasm becomes more marked

The Cyst. The cysts are spherical bodies varying from 4 to 20 μ in diameter Young cysts are uninucleate, possessing a large, rather coarse nucleus which may be one third the diameter of the cyst As nuclear division occurs, binucleate as well as the fully developed quadrinucleate forms are produced, the size of the individual nuclei decreasing as they increase in number.

In iron-hematoxylin stained preparations the hyaline single wall of the mature cyst is unstained and the cytoplasm appears grayish white The delicately beaded nuclear membranes and the karyosomes are deep black, and blunt-ended black-stained chromatoid bodies are occasionally present in the cytoplasm

In unstained fresh smears the colorless cytoplasm has a finely granular appearance, and the nuclei can only rarely be seen as delicate rings of *fine refractile granules. In young or immature cysts chromatoid bars* are commonly but not invariably observed These appear as blunt ended rods or rounded bodies having a different refractive index from the rest of the cyst They are distinctive and diagnostic

In iodine stained preparations the cysts of *E histolytica* can usually be differentiated from the cysts of the other intestinal protozoa The cytoplasm appears yellowish in color and occasionally contains a diffuse mass of glycogen staining mahogany brown The nuclei, which resemble gold wedding rings, are readily seen Although the chromatoid bodies may be visible they are more easily seen in the unstained or hematoxylin stained smears or in iodine stained preparations of *formalin ether concentrates*

As indicated in Tables VI 2 and VI 3, small races of *Entamoeba histolytica* occur In addition, small histolytica like forms with apparent morphologic differences have been described for which the name *E hartmanni* has been proposed *E hartmanni* is thought to be nonpathogenic The study required to distinguish between *E hartmanni* and small races of *E histolytica*, based upon the morphologic criteria employed, probably is not practicable for most laboratories performing routine stool examination From the practical standpoint, the interest of the patient should be borne in mind when the specific identity of small histolytica-like forms is uncertain The possibility of their being *E histolytica* definitely should be considered

Entamoeba coli

Entamoeba coli (Grassi, 1879) Casagrandi and Barbagallo 1895 is a common nonpathogenic ameba of the human colon Its importance lies in possible confusion with *E histolytica* Its presence in the stool provides evidence concerning the sanitary environment to which the host has been exposed The life cycle includes both trophozoite and encysted stages

The Trophozoite. The motile ameba averages 20 to 30 μ in diameter. In iron hematoxylin stained smears the single nucleus is relatively large and coarse. The nuclear membrane is thicker and the chromatin granules larger than in *E. histolytica*, whereas the karyosome is coarser. The cytoplasm is coarsely granular and typically contains many food inclusions such as bacteria, yeasts and detritus.

The living unstained organism is sluggishly motile, extending and withdrawing pseudopodia with little progressive motion. The pseudopodia are shorter and more blunt than those of *E. histolytica*. The nucleus is frequently visible, appearing as a large refractile ring containing a small hyaline mass representing the karyosome. This ameba rarely ingests red blood cells.

The Cyst. The cysts of *E. coli* are spherical or ovoid bodies usually ranging between 15 and 20 μ in diameter. The younger forms are uninucleate or binucleate. Successive nuclear divisions occur to produce the characteristic eight nuclei of the mature cyst; rarely there may be 16 to 32. The individual nucleus decreases in size and becomes more delicate with each division.

In iron hematoxylin stained smears the cyst wall is unstained. The nuclei may be larger than those of *E. histolytica*, the nuclear membrane is heavier, and the chromatin granules are coarser. The karyosome is relatively large. Chromatoidals are occasionally observed in immature cysts and characteristically appear as black staining splinter-like bodies or as masses with jagged ends.

In unstained fresh smears some of the nuclei are often visible. The chromatoid bodies likewise may be seen when present. The contour of the latter and the visibility of the nuclei in unstained preparations have diagnostic significance.

The ringlike nuclei are clearly shown in iodine stained smears and, when present, the glycogen mass stains a deep mahogany brown. The splinter-like chromatoid bodies usually do not appear.

Endolimax nana

Endolimax nana (Wenyon and O'Connor, 1917) Brug, 1918, is a small nonpathogenic ameba of man. Both trophozoite and encysted stages are known.

The Trophozoite. The trophozoite averages 8 to 10 μ in diameter. The structure of the spherical nucleus is characteristic and diagnostic in iron hematoxylin stained smears. The nuclear membrane lacks chromatin beading. The karyosome is large, irregular or lobulated in shape and may be central or eccentric in position. The cytoplasm is granular and vacuolated and contains bacteria, yeasts and other food inclusions. Red blood cells are not ingested.

In fresh unstained preparations the trophozoite is sluggishly motile, extruding and withdrawing short blunt hyaline pseudopodia, but exhibiting little progressive motion. Often round pseudopodia are present. These give the trophozoite the appearance of budding. The trophozoites of *E. nana* are approximately one half the size of those of *E. histolytica* (except the small race) and *E. coli*.

The Cyst The cysts are thin walled oval or spherical bodies varying from 7 to 10 μ in diameter The single nucleus of the young form undergoes division to produce the mature four nucleate cyst

The structure of the nucleus is clearly shown in iron hematoxylin stained preparations The absence of chromatin beads on the nuclear membrane and the large irregular eccentric karyosome are characteristic

The nuclei are usually not visible in fresh unstained preparations and chromatoid bars are absent *In iodine stained smears the nuclei appear* as punched out holes resembling small vacuoles A small dot representing the karyosome sometimes may be detected on the periphery of the vacuole like nuclear outline In contrast to *E histolytica* and *E coli* the nuclei do not appear ringlike in iodine stained smears

Iodamoeba bütschlii

Iodamoeba butschlii (v Prowazek 1911) Dobell 1919 is a nonpathogenic intestinal ameba of man Both *trophozoite and encysted stages* occur in its life cycle

The Trophozoite In iron hematoxylin stained preparations the *trophozoite averages 9 to 13 μ in diameter The large spherical nucleus* consists of an achromatic nuclear membrane and a very large deeply stained round karyosome The cytoplasm contains bacteria yeasts and other inclusions This ameba does not ingest red blood cells In unstained warm smears from freshly passed stools the ameba exhibits sluggish progressive motility and protruding broad hyaline pseudopodia

The Cyst The cysts are very irregular in shape a distinctive characteristic and vary from 6 to 15 μ in diameter The cysts are relatively thick walled usually uninucleate occasionally binucleate and characteristically contain a large round or oval sharply demarcated glycogen mass

In iron hematoxylin stained preparations the single nucleus presents a thin unbeaded nuclear membrane The large deeply stained round karyosome is often eccentrically placed and in contact with the nuclear membrane The position of the glycogen mass is indicated *by a large* vacuole

In unstained smears the nucleus is usually not visible and the glycogen mass appears as a vacuole

In iodine stained preparations the large sharply defined deep mahogany colored glycogen body is the most striking feature of the cyst The single nucleus usually does not appear ringlike Occasionally a small yellow mass representing the karyosome may be visible if not obscured *by the glycogen mass*

Dientamoeba fragilis

Dientamoeba fragilis Jepps and Dobell 1918 is known only in the trophozoite stage An encysted stage has not been identified and the exact means of transmission are in doubt

The Trophozoite This ameba varies *from 5 to 20 μ in* diameter A majority of the specimens seen are binucleate The structure is characteristic in iron hematoxylin stained preparations The nuclear membranes

f the two nuclei are very delicate and often invisible. The centrally placed coarse lobulated karyosome is composed of a group of chromatin granules. The two nuclei may be connected by a dark staining thread. The cytoplasm is granular and contains a variety of food inclusions. Red blood cells are not ingested.

1 2 3

Figure VI 3 Dientamoeba fragilis. 1 Uninucleate ameba. 2, 3 Binucleate amebae. (After Dobell and O'Connor in Craig, C. F.: Amebiasis and Amebic Dysentery. Charles C Thomas, Springfield, Ill.)

Table VI 4 Differentiation of Intestinal Amebae in Direct Fecal Smears of Unpreserved Fresh Stools

TROP[illegible]O[illegible]TES

Unstained Saline Smear (Fig. VI 4) [illegible]

1 (4) Trophozoites usually large (except for small races [illegible] E. histolytica) [illegible]

2 (3) Progressive motility with [illegible] finger-like shape [illegible] pod [illegible] E. histolytica [illegible] ingested red cells [illegible] stain [illegible]

3 (2) No progressive motility [illegible] does not flow into [illegible] retracted [illegible] E. coli [illegible] E. nana [illegible] frequently [illegible] formed [illegible]

4 (1) Trophozoites [illegible] rectangular or [illegible]

5 (6, 7) [illegible] often [illegible] perfectly round [illegible] D. fragilis

6 (5, 7) [illegible] I. butschlii [illegible]

7 (5, 6) [illegible] E. histolytica or E. coli [illegible]

Iodine Stained Smear [illegible] E. nana [illegible] I. butschlii [illegible] D. fragilis

1 (2) Ring-like [illegible] [illegible] (the above species must be [illegible] stained smears)

2 (1) Ring-like [illegible] (Differentiation [illegible])

[illegible]TS

Unstained Saline Smear (Fig. VI 4) [illegible] E. histolytica [illegible] Other [illegible]

1 (3) Chromatoid [illegible] (rod-like [illegible]) [illegible] Present [illegible] absent

3 (1) Chromatoid [illegible] always absent [illegible] E. histolytica [illegible] E. coli

Iodine Stained Smear (Fig. VI 5)

1 (4) Ring-like [illegible] 6–1[illegible] μ [illegible]

2 (3) Medium sized or small cyst [illegible] with less than 5 nuclei [illegible]

3 (2) Large [illegible] with 5 or more nuclei [illegible] (1 [illegible] cyst [illegible] finally the [illegible] cyst in sanies [illegible]

4 (1) [illegible] appearing as a vacuole-like [illegible] E. nana [illegible] absent

5 (6) Small [illegible] areas [illegible] I. butschlii

6 (5) Medium sized cyst with [illegible] sharply [illegible] from the cytoplasm

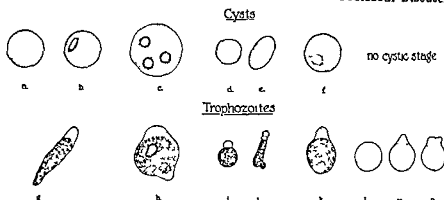


Figure VI.4 Cysts (a f) and trophozoites (g n) of common intestinal amebae in direct saline fecal smears fresh unpreserved unstained a. *Entamoeba histolytica* no nuclei visible b *E histolytica* with refractile chromatoid bar c *Entamoeba coli* with a few ringlike nuclei visible d e *Endolimax nana* small and round or elongate-oval. f *Iodamoeba butschlii* glycogen vacuole slightly refractile g Sluglike trophozoite of *E histolytica* nucleus not visible h *E coli*, nucleus visible i j Budlike pseudopodia of *E nana* k I *bütschlii* l *Dientamoeba fragilis*, spherical shape m,n *D fragilis* triangular and rectangular pseudopodia (Courtesy of C Swartzwelder in Am J Clin Path 22 1952)

In warm smears from freshly passed stools these amebae at first appear as immobile spherical bodies After a variable period sluggish, usually nonprogressive motility begins

The pseudopodia are clear, glasslike, sharply differentiated from the endoplasm and characteristically triangular, rectangular or clover leaf in outline The nuclei are rarely visible Motility ceases promptly on cooling, and the ameba rounds up into a spherical body

Giardia lamblia

The flagellate, *Giardia lamblia* Stiles, 1915 inhabits the duodenum, the upper jejunum and occasionally the gallbladder of man The life cycle comprises both trophozoite and encysted stages

The Trophozoite. This flag
pear in shape and measures 11 to
is convex dorsally and concave
occupying the anterior ventral surface There are eight flagella Multiplication occurs by longitudinal fission

The detailed structure is visible only in iron hematoxylin preparations A pair of axostyles, originating anteriorly from a pair of blepharoplasts, are continued backward to extend posteriorly as flagella The two anteriorly situated nuclei lie on either side of the axostyles Three additional pairs of flagella, an anterolateral, a posterolateral and a ventral, originate from the blepharoplasts The cytoplasm does not contain food inclusions or red blood cells

In fresh unstained preparations the trophozoite is actively motile, combining irregular progression, rotation and rocking movements The eight flagella become visible only as motility almost ceases The cytoplasm is hyaline or finely granular in appearance

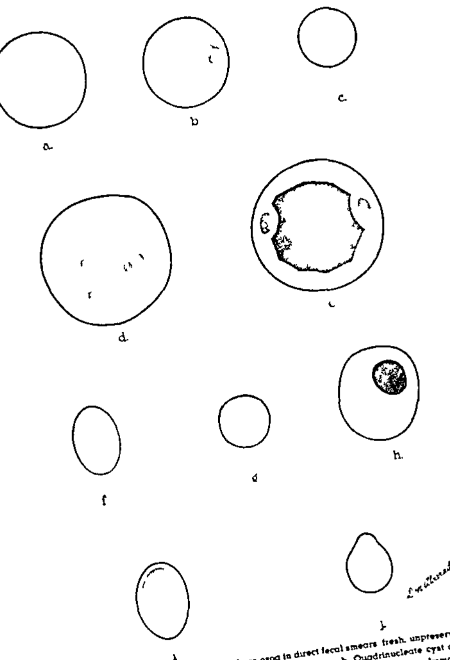


Figure VI.5 Cysts of some intestinal pro ozoa in direct fecal smears fresh, unpreserved iodine stained a. Uninucleate cyst of *Entamoeba histolyt ca* b. Quadrinucleate cyst of *E histolytica* c. Small race of *E. histolytica* d. Mature cyst of *En amoeba coli* e. Immature cyst of *E coli* f g *Endol max nana* h. *Iodamoeba bütschlii* i *G ard a lamblia* j *Ch omast mesn* i. (Courtesy of the Louisiana State University School of Medicine

The Cyst The cysts of *G lamblia* are ovoid in contour They measure 8 to 12 μ in length and 6 to 10 μ in width They contain two to four nuclei usually situated near one pole

In iron hematoxylin stained preparations the individual nucleus is seen to consist of a delicate nuclear membrane and a small central or eccentrically placed karyosome The axostyles appear as two longitudinally placed curved rods and the flagella as groups of stained fibrils

In unstained smears the cysts appear as ovoid colorless hyaline bodies with a thick cyst wall in which refractile structures representing the axostyles and flagella may sometimes be seen

In iodine stained smears the longitudinal axostyles and fibrils representing the flagella may be seen usually the nuclei are indistinct The cytoplasm stains a brownish color and may contain diffuse glycogen

Chilomastix mesnili

Chilomastix mesnili (Wenyon 1910) Alexeieff 1912 is a nonpathogenic flagellate inhabiting the large intestine of man It is frequently found in normal individuals in many parts of the world Both trophozoite and encysted stages occur in its life cycle

The Trophozoite This flagellate is 13 to 24 μ in length and 6 to 11 μ in breadth Occasionally minute almost spherical forms less than five microns in length are observed The typical specimen has a rigid pear shaped body with a spiral groove and is pointed at the posterior end Multiplication occurs by binary fission

In iron hematoxylin stained preparations the spiral groove is clearly visible The cytoplasm is finely granular A mouthlike cytostome appearing as a cleft originates anteriorly and extends posteriorly for nearly one half the length of the body The nucleus situated anteriorly near the point of origin of the cytostome has a well defined nuclear membrane and a small round centrally or eccentrically placed karyosome Three free anterior flagella and one oral flagellum originate from a blepharoplast complex in the anterior portion of the organism

In warm smears from freshly passed stools the trophozoites are actively motile progressing in a jerky spiral fashion The cytoplasm is colorless or faintly greenish In sluggishly motile specimens the three anterior flagella the cytostome and the spiral groove may be visible

The Cyst The cysts of *C mesnili* are ovoid in shape averaging 7 to 9 μ in length by 4.5 to 6 μ in breadth A blunt protuberance at one pole gives them a lemon shaped appearance There is a single spherical nucleus

In iron hematoxylin stained smears the nuclear membrane is distinct and the karyosome may be central or eccentric and in contact with the nuclear membrane The condensed cytostome is longitudinally placed in close proximity to the nucleus The flagella may appear as dark stained fibrils

In unstained preparations the cysts are colorless and the internal structures are not visible

In iodine preparations they are stained yellowish brown and the nucleus and cytostome may sometimes be faintly seen One or more small glycogen masses may rarely be demonstrated

Trichomonas hominis

Trichomonas hominis (Davaine, 1860) Leuckart, 1879

The flagellate, *Trichomonas hominis* (Davaine, 1860) Leuckart, 1879, is an inhabitant of the cecum or colon of man. It is widely distributed throughout the world. Only the trophozoite stage is known. *T. hominis* is nonpathogenic. When diarrhea of nonparasitic etiology occurs, the flagellate may flourish and become the predominant organism in the stool. It is possible that, under such conditions, *T. hominis* may prolong a diarrhea initially of other etiology. Symptomatic treatment to control the diarrhea results in reduction in the numbers of the trophozoites.

The Trophozoite. *Trichomonas hominis* is a pear-shaped flagellate possessing three to five anterior flagella and a distinct undulating membrane. It averages 10 to 14 μ in length. Reproduction is by longitudinal fission.

In iron hematoxylin stained preparations the single ovoid nucleus with central karyosome and delicate nuclear membrane is visible near the anterior or blunt end. A blepharoplast complex just anterior to the nucleus provides the origin of (1) the anterior flagella, (2) a marginal flagellum which shortly leaves the body to form the edge of the undulating membrane, and (3) an axostyle, which is continued longitudinally through the body and protrudes posteriorly for a variable distance.

In fresh unstained preparations it exhibits active, wobbly progressive motion due to the activity of the flagella and the undulating membrane. The nucleus and other internal structures are not visible in the colorless finely granular cytoplasm.

Trichomonas tenax

One other species, *T. tenax* (O. F. Muller, 1773) Dobell, 1939, has been found only in the human mouth, where it occurs in dental cavities, alveolar pus pockets, and in the tartar on the teeth. It is the only flagellate known to inhabit the human mouth and is nonpathogenic.

Trichomonas vaginalis

Although it does not inhabit the intestine, *T. vaginalis* Donne, 1837, is discussed here with related flagellates. The usual habitats of *T. vaginalis* are the vagina, urethra, and the prostate gland. This flagellate is observed much more frequently in women than in men. It is pathogenic and may be associated particularly with a form of vaginitis. It is widely distributed throughout the world. Multiplication occurs by longitudinal fission. This organism is known only in the trophozoite stage.

The Trophozoite. *Trichomonas vaginalis* closely resembles *T. hominis*. It is larger, measuring 10 to 30 μ in length; there are four anterior flagella, and the undulating membrane is shorter than that of *T. hominis*, extending only about one half the length of the body, where the marginal flagellum terminates. There is no free posterior flagellum.

Although the three species of *Trichomonas* have distinct morphologic and biologic differences, all possess an undulating membrane. When motility of trichomonads is sufficiently slow, the rippling wavelike

tion of the undulating membrane may be observed For practical purposes, the presence of an undulating membrane on a flagellate in (1) vaginal secretion, urine or prostatic fluid, (2) stool and (3) material from the oral cavity is sufficient to identify it as to species by its source *T vaginalis*, *T hominis* and *T tenax*, respectively

Balantidium coli

Balantidium coli (Malmsten 1857) Stein, 1862 is the only ciliate pathogenic for man It inhabits the large intestine and less commonly the lower portion of the ileum *Balantidium coli* is widely distributed throughout the world Forms morphologically indistinguishable from *B coli* in man parasitize the pig, various species of monkeys and rats Both trophozoite and encysted stages occur in its life cycle

The Trophozoite. *Balantidium coli* is the largest of the protozoan parasites of man, 50 to 70 μ in length by 30 to 60 μ in breadth It is ovoid in shape and actively motile Multiplication occurs by transverse binary fission and by conjugation of two trophozoites

In iron hematoxylin stained preparations the external surface is seen to be covered with cilia arranged in longitudinal rows The oral apparatus or peristome is a V shaped groove or depression at the anterior end lined by somewhat larger cilia The mouth lies at the base of this structure, opening into the gullet A large kidney shaped macronucleus and a smaller micronucleus usually in apposition to the concave surface of the former, are situated in approximately the central portion of the body There are two contractile vacuoles, one anterior and one posterior The cytoplasm contains a variety of food inclusions including red blood cells, leukocytes, starch granules and bacteria

In unstained fresh smears the trophozoite moves actively with a smooth gliding motion The rapidly beating cilia cannot be seen The macronucleus often is visible, but the micronucleus is not readily discerned

The Cyst. The cysts of *B coli* are oval, measuring 50 to 65 μ in greatest diameter, and the cyst wall appears to have a double outline They stain poorly with either iodine or hematoxylin although the nuclei and the unstained contractile vacuoles are easily seen

In unstained preparations the organism may show motility within the cyst wall The cytoplasm has a faintly greenish tinge The macronucleus and the contractile vacuoles may be faintly visible

Isospora belli

Isospora belli Wenyon, 1923 is a relatively uncommon sporozoan parasite of man Although *I belli* is believed to inhabit the ileum, the finding of oocysts in duodenal drainage fluid suggests that the sites of infection may include the duodenum and possibly the biliary tract Although details of the development of *Isospora* species in man are unknown, they are presumed to resemble those of coccidia of the dog and cat Schizogonic development presumably occurs in the epithelial or subepithelial levels of the intestinal mucosa Gametocyte formation and eventual development of oocysts is believed to take place in the lumen of the intestine Maturation of the oocyst occurs as the inner granular

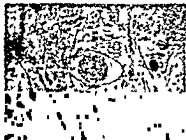


Figure VI 6



Figure VI 7

Figure VI 6 Immature oocyst of Isospora belli from freshly passed feces (1000 ×) (Courtesy Dr T B Magath Mayo Clinic)

Figure VI 7 Older oocyst of *Isospora belli* showing two sporoblasts (1000 ×) (Courtesy Dr T B Magath Mayo Clinic)

nuclear mass divides to form two sporoblasts Each of these in turn secretes a wall and becomes a sporocyst The nuclear material within each sporocyst divides twice to produce four crescentic sporozoites Upon ingestion of the infective oocysts the sporozoites escape and invade the mucosal cells where schizogony and sporogony occur

The Oocysts These are ovoid and somewhat elongated and measure 30 by 12 μ They may be passed at all stages of development immature forms mature in up to five days The contained sporocysts measure 11 by 9 μ Typically there is no oocystic residual body The sporocystic residual body is finely granular with a limiting membrane that is compact and centrally located between the four sporozoites (Figs VI 6 VI 7 VI 8)

Isospora hominis

In contrast to *I belli* the oocysts of *I hominis* (Rivolta 1878) Dobell 1919 ordinarily are passed fully developed and the oocyst wall is usually absent The sporocysts may be single or coupled in pairs each being 15 by 10 μ The sporocystic residual body is composed of coarse loosely aggregated granules that appear polar in position and separate from the four sporozoites (Fig VI 8)

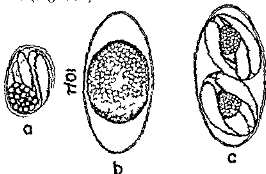


Figure VI 8 a Single sporocyst of *Isospora hominis* b Immature oocyst of *I belli* c Mature *I belli* oocyst (Courtesy of Dr R Elsdon Dew)

tion of the undulating membrane may be observed For practical purposes, the presence of an undulating membrane on a flagellate in (1) vaginal secretion, urine or prostatic fluid, (2) stool and (3) material from the oral cavity is sufficient to identify it as to species by its source *T vaginalis*, *T. hominis* and *T tenax*, respectively

Balantidium coli

Balantidium coli (Malmsten, 1857) Stein, 1862 is the only ciliate pathogenic for man It inhibits the large intestine and less commonly the lower portion of the ileum *Balantidium coli* is widely distributed throughout the world Forms morphologically indistinguishable from *B coli* in man parasitize the pig, various species of monkeys and rats Both trophozoite and encysted stages occur in its life cycle

The Trophozoite. *Balantidium coli* is the largest of the protozoan parasites of man, 50 to 70 μ in length by 30 to 60 μ in breadth It is ovoid in shape and actively motile Multiplication occurs by transverse binary fission and by conjugation of two trophozoites

In iron-hematoxylin stained preparations the external surface is seen to be covered with cilia arranged in longitudinal rows The oral apparatus or peristome is a V shaped groove or depression at the anterior end lined by somewhat larger cilia The mouth lies at the base of this structure, opening into the gullet A large kidney-shaped macronucleus and a *smaller micronucleus, usually in apposition to the concave surface of* the former, are situated in approximately the central portion of the body. There are two contractile vacuoles, one anterior and one posterior The cytoplasm contains a variety of food inclusions, including red blood cells, leukocytes, starch granules and bacteria

In unstained fresh smears the trophozoite moves actively with a smooth gliding motion The rapidly beating cilia cannot be seen The macronucleus often is visible, but the micronucleus is not readily discerned

The Cyst. The cysts of *B coli* are oval, measuring 50 to 65 μ in greatest diameter, and the cyst wall appears to have a double outline. They stain poorly with either iodine or hematoxylin although the nuclei and the unstained contractile vacuoles are easily seen

In unstained preparations the organism may show motility within the cyst wall The cytoplasm has a faintly greenish tinge The macro nucleus and the contractile vacuoles may be faintly visible

Isospora belli

Isospora belli Wenyon, 1923 is a relatively uncommon sporozoan parasite of man Although *I belli* is believed to inhabit the ileum, the finding of oocysts in duodenal drainage fluid suggests that the sites of infection may include the duodenum and possibly the biliary tract Although details of the development of *Isospora* species in man are unknown, they are presumed to resemble those of coccidia of the dog and cat Schizogonic development presumably occurs in the epithelial or subepithelial levels of the intestinal mucosa Gametocyte formation and eventual development of oocysts is believed to take place in the lumen of the intestine Maturation of the oocyst occurs as the inner granular

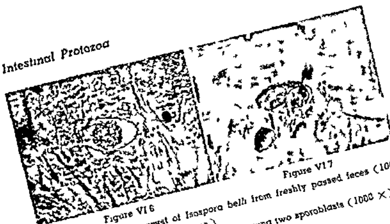


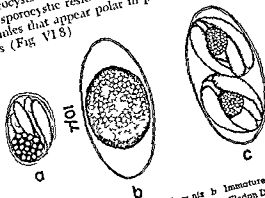
Figure VI.6 Immature oocyst of *Isospora belli* from freshly passed feces (1000 ×) (Courtesy Dr T B Magath Mayo Clinic)
Figure VI 7 Older oocyst of *Isospora belli* showing two sporoblasts (1000 ×) (Courtesy Dr T B Magath Mayo Clinic)

nuclear mass divides to form two sporoblasts Each of these in turn secretes a wall and becomes a sporocyst The nuclear material within each sporocyst divides twice to produce four crescentic sporozoites Upon ingestion of the infective oocysts the sporozoites escape and invade the mucosal cells where schizogony and sporogony occur

The Oocysts. These are ovoid and somewhat elongated and measure 30 by 12 μ They may be passed at all stages of development immature forms mature in up to five days The contained sporocysts measure 11 by 9 μ Typically there is no oocystic residual body The sporocystic residual body is finely granular with a limiting membrane that is compact and centrally located between the four sporozoites (Figs VI 6 VI 7 VI 8)

Isospora hominis

In contrast to *I belli* the oocysts of *I hominis* (Rivolta 1878) Dobell 1919 ordinarily are passed fully developed and the oocyst wall is usually absent The sporocysts may be single or coupled in pairs each being 15 by 10 μ The sporocystic residual body is composed of coarse loosely aggregated granules that appear polar in position and separate from th four sporozoites (Fig VI 8)



VI 8 a Single sporocyst of *Isospora hominis* b Immature oocyst of *I belli* oocyst (Courtesy of Dr R Elsdon Dew)

Blastocystis hominis

The yeast, *Blastocystis hominis*, although a nonpathogenic commensal in the digestive tract of man, is included because it may be mistaken for encysted forms of intestinal protozoa

It is ovoid or spherical in shape, averaging 10 to 15 μ in greatest diameter, and occasionally reaches a considerably larger size The hyaline refractive cytoplasm is included within a membrane resembling a cyst wall The outer layer of cytoplasm immediately adjacent to the membrane is frequently differentiated, creating the appearance of a double-walled cyst This outer layer contains refractile granules and one or more nuclei which are visible in unstained preparations The central portion is structureless and resembles a large vacuole Dividing forms are common and exhibit marked variation in size and shape

In iron hematoxylin stained preparations the central cytoplasmic mass appears grayish in color, the peripheral band is unstained except for the nuclei and their large centrally placed karyosomes Iodine also stains the nuclei, and the central cytoplasm may appear clear or brownish in color (Fig VI 2, p 255)

34

Amebiasis and Related Infections

Amebiasis

Synonyms. Amebic dysentery, amebic enteritis amebic colitis

Definition. Amebiasis is an infection by the pathogenic ameba, *Entamoeba histolytica* Intestinal amebiasis is characterized by acute or chronic phases, or both, and by a variable clinical picture The so called chronic cyst-passer may exhibit few or no significant symptoms In other instances infection may be characterized by *intermittent episodes of* constipation and diarrhea, in still others the diarrhea may be relatively [illegible] ...us Acute ...es but is ...s of this infection may be followed promptly or after prolonged periods by the serious complications, amebic hepatitis or amebic abscess of the liver Less frequently metastatic abscesses occur in other organs

...ebiasis and Related Infections

Distribution Amebiasis has a cosmopolitan distribution and is not restricted to the tropics. Epidemics of amebiasis have occurred in temperate areas such as the United States, Japan and Korea. The prevalence in any population is determined by the level of sanitation existing in the particular areas.

Etiology *Entamoeba histolytica* is the most important of the intestinal protozoa of man. Its life cycle has three distinct stages. The cyst is the infective stage and is ingested in food and drink. Both the mature four nucleate cysts and the immature cysts are infective. As the cysts pass through the intestine they are acted upon by the digestive secretions. They excyst in the small intestine and the trophozoites that emerge usually are four nucleate amebae which soon divide into uninucleate trophozoites. The uninucleate trophozoite is the actively growing and multiplying stage. Multiplication is by binary fission and two uninucleate trophozoites form from the parent ameba. These actively growing trophozoites may invade the tissue of the large intestine producing colonies in the intestinal wall and ulcerative lesions.

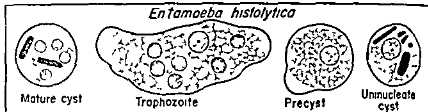
Cysts are formed as the trophozoites are carried in the lumen contents toward the rectum where the fecal material is dehydrated, but the exact stimulus that produces cyst formation is not known. The mature trophozoite first eliminates food vacuoles and other cytoplasmic inclusions and becomes a precystic ameba. The precystic form then secretes a cyst wall forming a uninucleate immature cyst, which continues to develop as a rule to the typical four nucleate cyst. This entire cycle takes place within the intestinal tract of man and a few other animals. Cysts of some strains of *Entamoeba histolytica* develop in suitable culture media. Cysts do not develop in the tissues nor from trophozoites after passage from the body. Immature cysts may mature outside the body under favorable conditions.

Epidemiology The actively motile trophozoites present in the freshly passed feces of patients suffering from amebic diarrhea or dysentery are short lived outside the body. It is unlikely that they can survive exposure to the hydrochloric acid and digestive enzymes of the stomach and upper intestinal tract. They are therefore of little if any importance in the transmission of the disease.

The encysted forms however are resistant to marked changes in their environment and are responsible for transmission. The infection is acquired by the ingestion of these encysted forms in food or drink contaminated by the feces of infected individuals.

The cysts of *E. histolytica* are readily destroyed by drying; they are also killed rapidly at 55° C. They will survive as long as one month in water at about 10° C. The cysts are relatively resistant to chlorine and are not destroyed by concentrations customarily used for water purification. If dependence is to be placed upon chlorination alone the concentration and contact time must be adjusted in accordance with the temperature and hydrogen ion concentration of the water.

Dilute disinfectants as ordinarily used are not markedly effective in destroying the encysted forms. In moist feces survival time is rec... to approximately 12 days and is controlled by the rate of putref...



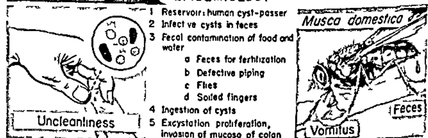


Figure VI 9 Epidemiology of amebiasis

and the temperature At 4° C cysts remain viable for at least 60 days in both sewage and natural surface waters

Man is the principal reservoir of infection However, amebae which are morphologically similar to *E histolytica* have been recovered from the dog, cat, rat, pig and various types of monkeys

Transmission of the infection from one individual to another may be

accomplished by a variety of mechanisms (Fig VI 9) The infected individual passing large numbers of cysts in his stools is an important potential source of infection especially if engaged in the preparation and handling of food There are numerous instances especially in family outbreaks which indicate the hazard of such employment of the cyst passer

The housefly and the cockroach feed upon human feces when available and cysts of *E histolytica* have been recovered from the intestinal tracts of these insects apparently undamaged after periods as long as 48 hours In some areas flies probably are important in the epidemiology of amebiasis (Fig VI 9)

Polluted water may likewise be an important vehicle of infection Fecal contamination of water commonly occurs by surface run off into springs unprotected shallow wells and streams or by discharge of crude sewage into streams and rivers Less frequently cross seepage between water and sewer pipes laid in the same ditch or direct cross connections with siphonage of sewage into the water supply system are responsible for outbreaks of infection The freshening of vegetables before sale is widely practiced in many parts of the world In many regions human excreta night soil is widely used as garden fertilizer This practice may be responsible for heavy contamination of root and leafy vegetables which customarily are eaten raw

Epidemic outbreaks of amebiasis are uncommon and all reported instances have been traced to a heavily contaminated water supply or to

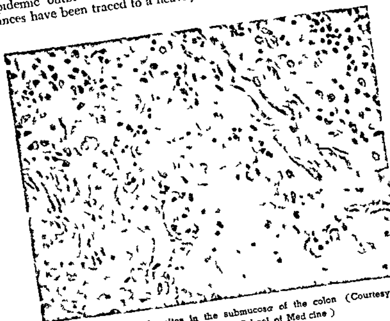


Figure VI 10 Amebic trophozoites in the submucosa of the colon (Courtesy Louis and State University School of Medicine)

Figure VI 11.





Figure VI 12

Figure VI 11. Amebic ulcers of the large intestine Note raised margins of ulcers (Courtesy of The Louisiana State University School of Medicine)

Figure VI.12. Section of colon showing flask shaped chronic amebic ulcer involving [illegible] te [illegible] g

field III)

fly transmission The disease occurs characteristically in endemic form The infection rate is low in young children, but in the school age group the incidence reaches that of the general population of the area in which they live

Pathology. The fundamental pathology of amebiasis is characterized by penetration of the host's tissues by *E histolytica*, necrosis of tissue cells, and absence of inflammatory reaction

Lesions are most commonly found in the cecum, ascending colon, sig-

eventually opening through the surface to produce the characteristic flask or bottle neck ulcer (Figs VI 11, VI 12) Both the superficial and the deeper lesions may form the "sea anemone" ulcer with a deep crater and partly necrotic undermined edges which are raised above the level of the surrounding mucosa (Fig VI 13)

Initially there is little edema and no leukocytic response Secondary bacterial infection of the ulcers occurs rapidly, however, producing a varying, severe inflammatory reaction Occasionally shigellosis is super imposed, rarely secondary infection by *Cl perfringens* may produce a rapidly spreading and fatal gangrene of the colon In some instances, extensive and rapid invasion of the colonic wall by the amebae may lead to severe or fatal hemorrhage or perforation The resulting ulcer, the so-called 'Dyak hair" ulcer, is sharply circumscribed, and the base is formed by fringelike projections of the more resistant supporting tissues (Figs VI 14, VI 15)

The characteristics of the stool mirror the pathologic process in the colon In the presence of the "Dyak hair" type of ulceration, hemorrhage is usual, in less severe cases of dysentery the stools are foul and usually bloody In milder infections there may be little abnormality, or small flecks of blood stained mucus intimately mixed with liquid feces produce the so called sago grain" stools

On microscopic examination of the particles of mucus the cellular exudate is characteristic Leukocytes are considerably less numerous than in shigellosis Erythrocytes are often found clumped Eosinophils and pyknotic bodies may be present in the dysenteric exudate Con versely, peripheral eosinophilia of the blood is not characteristic of amebiasis Leukocytes appear and increase in numbers in the stool as secondary bacterial infection of the ulcers occurs and extends Macro phages are not seen in the absence of infection by a member of the genus *Shigella*, except after arsenical therapy

Invasion of the submucosa may be followed by entry of *E histolytica* into radicles of the portal vein and metastasis of the infection to the liver This is followed by amebic hepatitis or amebic abscess of the liver Such abscesses may be single or multiple, acute or chronic Multiple foci of necrosis may coalesce to form a single large abscess Leukocytic infiltration of the wall occurs even in the absence of secondary bacterial



Figure VI 13



Figure VI 14

Figure VI 13 Sea anemone ulcers of colon
Figure VI 14 Dyak hair ulcers of colon showing superficial and deep ulceration

infection Right lobe abscesses of the liver commonly extend upward and may penetrate the diaphragm and rupture into the lungs Amebic abscess of the brain and other organs occurs rarely secondary amebic infections of the skin and subcutaneous tissues the bladder uterus and vagina have been reported

Clinical Characteristics The clinical response to infection by *E histolytica* is exceedingly variable and depends upon the localization of the amebae the intensity of the infection possibly differences in virulence of strains bacterial flora and other factors The ratios of amebic abscess of the liver acute dysentery and diarrhea to the known prevalence of amebic infection in the population are low It is generally recognized that frank amebic dysentery is more common in the tropics and subtropics than elsewhere and that in the temperate zones it is more prevalent in the warmer months of the year

Large and small races of *E histolytica* have been identified The small races tend to be less pathogenic Although it may be possible for some small and large races of *E histolytica* to exist for a time as commensals in the lumen of the intestine the assumption that such races generally lack potential pathogenicity seems unwarranted From the practical standpoint of the clinician and patient such an assumption may be unwise since the commensal state may be altered by changes in diet or other factors with resultant tissue invasion and severe clinical disease It appears that virulence of *E histolytica* may be augmented by repeated serial passage

Infection by this parasite may persist for many years running a protracted course that is frequently characterized by periodic exacerba

tion of intestinal symptoms and by remissions during which the patient may be largely if not entirely free of symptoms

The Cyst Passer The cyst passer is the commonest clinical type Two classes are recognized convalescents who following acute dysentery or amebic diarrhea retain a chronic infection and more or less continuously show encysted forms in their stools and those who have acquired the infection but have not experienced active clinical disease

The relationship between the asymptomatic carrier state and active disease is controversial Some authorities state that not more than 10 per cent of cyst passers have clinical manifestations from the infection Others hold that at least 50 per cent exhibit symptoms attributable to *E histolytica* The problem is complicated by the fact that symptoms when present may be extremely variable and many of them cannot be considered as specific responses to the infection It is known that infected individuals may be essentially symptom free for periods of years only to develop without warning acute involvement of the liver with hepatitis or actual abscess formation Therefore it appears desirable to regard the infected individual not only as a source for potential spread to others but also as a person who may at any time develop acute symptoms and serious disease

The clinical picture of the chronic cyst passer characteristically lacks specificity and is extremely variable Some individuals are often apparently healthy while in others the most striking features are chronicity mildness and recurrence of symptoms The onset is usually insidious and frequently there are alternating periods of ill health and relative well being During the former abdominal distention and flatulence accom



Figure VI 15 Invasion of muscularis along penetrating vessel (Collection of Dr W M James and Dr Lawrence Getz)

panied by constipation are common complaints Although the constipation may be interrupted by occasional brief periods of loose stools these ordinarily do not attract attention especially since gross blood and mucus are not present in the feces These symptoms are commonly accompanied by vague abdominal discomfort and sense of abnormal fullness of the abdomen particularly on the right side Many individuals are irritable unduly *susceptible to fatigue and exhibit the lassitude and other phe*nomena associated with neurasthenia The relationship of some of the latter complaints to amebic infection has not been established

Amebic Diarrhea When the host parasite balance is less exact periodic bouts of diarrhea occur with several loose or liquid stools a day Abdominal discomfort and cramps may be present tenesmus does not occur and fever is usually absent There is usually little change in the white blood count although there may be a slight leukocytosis Careful examination of the stools commonly will reveal small flecks of blood tinged mucus in which there are large numbers of trophozoites The spontaneous cessation of diarrhea is usually followed by a variable period of constipation during which the vague symptoms of the cyst passer dominate *the clinical picture*

Amebic Dysentery Acute amebic dysentery is one of the less common clinical manifestations of intestinal amebiasis The incubation period may be as short as eight to ten days and in approximately 50 per cent of cases the onset is sudden This is especially true of mixed infections with *Shigella* In other instances acute dysentery may occur in the previously asymptomatic cyst passer who has carried his infection for long periods

When the onset is acute it may be accompanied by headache nausea chills fever severe abdominal cramps and if there are lesions of the *descending colon by tenesmus Some degree of enlargement of the liver* with tenderness on palpation occurs in approximately 25 per cent of cases The stools consist of liquid fecal matter containing flecks of bloody mucus the so called sago grain stools The white blood count may vary from 5000 to 15 000 with a polymorphonuclear leukocytosis as high as 85 per cent The fever tends to be lower and the leukocytosis slightly higher in acute amebic dysentery than in acute bacillary dysentery

In very severe cases extensive involvement of the colon may lead to massive destruction of the mucosa and the formation of a pseudodiphtheritic membrane which may be passed intact or actual gangrene of large portions of the colonic wall may occur In severe cases the deeply penetrating ulceration may produce serious or even fatal hemorrhage Usually however death when it occurs is due to cardiac failure and exhaustion or to perforation of the colon and peritonitis

Repeated and inadequately treated attacks of acute dysentery or of amebic diarrhea may be followed by chronic dysentery This is the result of long continued mixed infection of the colonic wall by *E histolytica* [illegible] progressive scarring and deformity [illegible] m chronic bacillary dysentery [illegible] is characterized by recurrent acute attacks of fever and by diarrhea with blood and pus in the stools *In the intervals* between acute attacks the stools are generally loose

increased in number and mixed with variable amounts of blood mucus and pus Chronic dysentery is commonly accompanied by malnutrition and cachexia

Ulcerative colitis carcinoma of the large intestine and colonic dysfunction of other etiology may simulate chronic amebic dysentery and cells in the exudate in these conditions may be confused with amebae

Amebic Appendicitis Infection of the appendix by *E histolytica* may occur and with secondary bacterial invasion the clinical picture of subacute appendicitis may be encountered In instances when the appendix occupies a retrocecal position the clinical picture may be exceedingly confusing Demonstration of *E histolytica* in the patient s stools however should be regarded as potentially significant evidence and in the absence of imperative indications for operation antiamebic therapy should be given before laparotomy is decided upon

Amebic Typhlitis In certain individuals the localization of the amebae remains principally restricted to its primary site in the cecum and ascending colon and the disease is limited principally to this area Under such conditions and in the presence of a progressive infection the clinical picture may be that of an acute or chronic typhlitis rather than acute dysentery and may arouse grave suspicion of a lesion in the right lower quadrant requiring surgical correction Operative procedure upon such infected tissue will almost invariably result in the breakdown of suture lines thus causing fatal peritonitis

Amebic Granuloma In certain instances intestinal amebiasis is accompanied by the formation of granulomatous lesions of the colon which are commonly misdiagnosed as carcinoma They may occur in any area from the cecum to the rectum Those that can be visualized through the sigmoidoscope may present many of the characteristics of adeno carcinoma In other instances roentgen examination following a barium enema may reveal a picture characteristic of an annular carcinoma pro ducing partial or even complete obstruction of the colon

Coincidental Amebic Infection Any infection like amebiasis that is prevalent in a significant proportion of the population at times may be present but coincidental to another infection or disorder in the same patient Thus amebiasis may occur in persons with carcinoma ulcerative colitis shigellosis psychoneurosis colonic dysfunction of psychosomatic origin or other conditions The possibility that the amebiasis may not be the primary cause of any or all of the patient s complaints should be borne in mind This is particularly true when bleeding or other findings and complaints continue after a reasonable amount of antiamebic ther apy has been employed for patients in whom *E histolytica* initially had been demonstrated

Diagnosis The diagnosis of intestinal amebiasis depends upon demonstration of *E histolytica* in the feces of the infected person If the individual is passing formed stools ordinarily only cysts will be found In the rare instances of active ulceration predominantly confined to the rectum however trophozoites may be found in flecks of blood stained mucus adherent to the surface of the stool If there is active diarrhea or acute dysentery on the other hand only the trophozoites are to be ex

pected These do not survive long after passage from the body and especially when exposed to chilling rapidly lose the motility and normal morphologic characteristics upon which identification must be based (Table VI 5) The detailed morphology is described on page 259 In contrast to the lack of need for haste in examining a formed specimen a diarrheal stool must be kept warm and examined at the earliest possible moment unless the PVA or MIF technique is employed (see pp 814 807)

Examination of Formed Stool A small portion of the excreta should be emulsified in saline solution on a glass fecal slide and covered with a coverslip The preparation should be of a density that just permits the reading of news print through it A similar fecal emulsion should be made with D Antoni s iodine solution on the same slide

In the unstained suspension the cysts of *E histolytica* appear as pearl like round refractile bodies in which no nuclei are visible or in which the nuclei can barely be distinguished When the condenser of the microscope is racked down the characteristic and diagnostic blunt ended chromatoid bar may be seen in some cysts in some but not all infections

In the iodine suspension the ringlike nuclei are easily visible These are four in number in the mature cysts but it is not unusual to observe younger forms which are uninucleate or binucleate Chromatoid bars are usually less frequently seen than in a water or saline suspension (p 260)

The laboratory diagnostician should require that objects observed in fecal smears or sigmoidoscopic aspirate meet the accepted morphologic criteria for *E histolytica* Otherwise cells or artefacts present in almost any specimen may be mistaken for this ameba

In light infections demonstration of the cysts is facilitated by con centration methods The formalin ether centrifugal concentration tech nique is a desirable supplement to direct fecal smears for routine stool examination These techniques are described in the section on Diagnostic Methods pp 809–810

Examination of Diarrheal Stool The freshly passed stool should be kept at body temperature by immersion of the container in warm water unless examination can be carried out immediately after evacuation Refrigeration or incubation (at 37° C) of liquid or formed stools usually has a deleterious effect on trophozoites and cysts A small quantity of liquid feces should be poured into a petri dish and carefully scrutinized for small flecks of blood stained mucus Such a particle of mucus should be placed on a slide covered with a coverglass and examined imme diately In the presence of an active amebic infection many of the flecks of bloody mucus contain large numbers of motile trophozoites which appear as elongated ribbon like amebae exhibiting progressive motion across the microscopic field The glasslike pseudopodia and the charac teristic progressive motion are diagnostic *E histolytica* trophozoites in dysenteric exudates frequently contain ingested red blood cells Con versely trophozoites in diarrheal stools without gross blood often con tain no red blood cells It is to be emphasized that the amebae are much

more numerous in the flecks of mucus than in the fecal material of the stools *Entamoeba histolytica* may be isolated in culture (pp 820–822)

Charcot Leyden crystals are frequently present in the stools Although suggestive they are not pathognomonic of infection by *E histolytica* since they occur in association with other parasitic infections and with any chronic ulcerative condition of the colon (Fig VI 16)

Proctoscopic Examination Proctoscopic or sigmoidoscopic examination of the chronic cyst passer seldom yields information of value In the more active clinical types of infection however lesions may be observed which are characteristic These are small discrete inflamed areas scattered about an otherwise normal mucous membrane They appear as isolated superficial erosions pits small nodules with a petechial ulceration on their surface or as yellow spots surrounded by a narrow band of hyperemia Immediate microscopic examination of the contents expressed with a spatula or aspirated with a glass tube and rubber bulb through the proctoscope will reveal trophozoites Cysts usually are not found in proctoscopic material

Biopsy scrapings may be obtained from the rectal mucosa by a long handled Volkmann spoon manipulated through a proctoscope under proper illumination The material in the bowl of the spoon should be placed on a slide immediately compressed under a coverglass and examined for *E histolytica* trophozoites Confusion of amebae with the cellular elements in the exudate and mucosal tissue must be avoided

Trophozoites can also be identified readily in hematoxylin eosin stained slides in a high percentage of punch or snip biopsies of amebic ulcers of the rectum All fragments of tissue and the adherent mucus

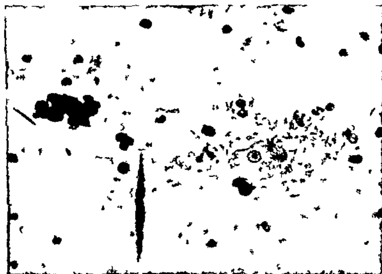


Figure VI 16 Early exudate in stool (iron hematoxylin stain) showing trophozoite clumped erythrocytes pyknotic bodies and Charcot Leyden crystals

should be included when preparing the tissue block Biopsy of rectal ulcers should be employed as a supplement, not a substitute, for examinations of stools and material aspirated during proctoscopy In selected cases where large ulcers are present, biopsy may be employed effectively for differential diagnosis between amebiasis and lesions of other etiology

X-ray Examination Roentgen examination of the colon is not a dependable aid in diagnosis since demonstrable lesions are by no means always present However, in acute cases, the barium enema may reveal spasm and evidence of ulceration, particularly in the proximal colon, and some degree of deformity of the cecum is not unusual in long standing chronic infections In the presence of amebic granuloma a filling defect suggestive of carcinoma may be seen

Culture Many strains of *E histolytica* may be cultured on Boeck Drbohlav or other suitable media (p 820) However, some strains are difficult or impossible to culture Culture technique for intestinal amebiasis is a supplemental procedure which may be employed with benefit in selected cases, particularly when large amebic trophozoites are encountered the identity of which cannot be determined owing to lack of motility Cultures of stools for *E histolytica* seldom yield positive results when a thorough microscopic examination has failed to demonstrate the presence of the ameba

Complement Fixation A reliable complement fixation test has not been developed When performed under optimal conditions, however, it may be of assistance in cases of extraintestinal amebiasis It does not give dependable results when infection is limited to the intestine

Table VI.5. Diagnostic Characteristics of *Entamoeba histolytica*

	FORM	WHERE FOUND	MORPHOLOGY
Liquid stools	Trophozoites	Blood stained mucus or feces	Progressive motion glasslike pseudopodia may contain red blood cells
Formed stools	Cysts	In the fecal mass	Saline preparation Blunt-ended chromatoid visible nuclei not visible except after formalin fixation Iodine preparation 1–4 nuclei at different levels chromatoid usually not visible except after formalin fixation
Semiformed stools	Cysts and/or trophozoites	In the fecal mass	Same as above

Treatment. Basic to the problem of therapy in amebiasis are the nature of the pathologic process and the natural habits of the parasite Some of the trophozoites reside in the intestinal contents, some are found on the surface of the mucosa, and others are found at various depths within the bowel wall or in other organs of the body The location of the amebae both in the lumen and deep in the tissues make it necessary to deliver an active amebicide in adequate concentrations to the tropho

zoites in the intestinal contents and in the tissues Amebic therapy is directed to the trophozoites not the cysts The various amebicides now in use vary considerably in their pharmacology and sites of action A careful selection of drugs is necessary in order to eliminate the amebae from the intestinal contents of the bowel and from the tissues wherever the lesions occur

Drugs The recommended drugs fall into several groups based upon their chemical composition

1 ARSENICALS *Carbarsone* p carbamido benzene arsonic acid is a pentavalent arsenical containing approximately 28 per cent arsenic It is readily absorbed excreted rather slowly in the urine and rarely produces ill effects at normal therapeutic levels The drug is active against amebae in the lumen and in the shallow lesions of the colon It is contraindicated in the presence of disease of the liver or kidneys and in patients intoler ant of arsenic

Milibis bismuth glycolylarsanilate contains approximately 15 per cent arsenic and 42 per cent bismuth It is absorbed only slightly from the intestinal tract Milibis like Carbarsone is an effective drug for the treatment of intestinal amebiasis but similarly ineffective against extra intestinal forms of the disease Contraindications are like those of Carbarsone

2 HALOGENATED HYDROXYQUINOLINES *Diodoquin* 5 7 diiodo 8 hy droxyquinoline contains 63 9 per cent iodine It is relatively insoluble and acts primarily on the lumen dwelling trophozoites It is most effec tive in asymptomatic and carrier patients and effective in combination with other amebicides in acute amebic dysentery Very few side effects have been noted This is a very useful drug in the treatment of either adults or children

Vioform 5 chloro 7 iodo 8 hydroxyquinoline contains 41 per cent iodine and 12 per cent chlorine It is the most readily absorbed of the hydroxyquinolines producing high blood levels which reach a peak about the seventh day of treatment It is somewhat irritating to the gastrointestinal tract and may cause a mild diarrhea in some individuals Contraindications are the same as for the other iodine drugs

Chiniofon (Anavodin Quinoxyl Yatren) 5 iodo 8 hydroxyquinoline contains 26 to 28 per cent iodine This drug is relatively insoluble and blood iodine levels of therapeutic importance do not occur Despite this chiniofon should not be used in patients with hyperthyroidism and is contraindicated in iodine sensitive individuals The drug may cause diarrhea in some patients

3 4 AMINOQUINOLINES *Chloroquine* (Aralen Nivaquine Alvochlor) is supplied as chloroquine diphosphate in tablet form Each 0 5 gram of the salt is equivalent to 0 3 gram of the base It is rapidly absorbed

widely used in the treatment of amebic liver abscess The use of com bined chloroquine and emetine hydrochloride therapy has resulted in

healing of extraintestinal lesions when the same drugs used alone failed Chloroquine is somewhat less effective but much less toxic than emetine The drug is well tolerated but in some individuals it may cause mild headache slight visual disturbances pruritus mild gastrointestinal symptoms and occasional psychic stimulation

Amodiaquin Camoquin (4[3 diethylamino methyl 4 hydroxyanilino] 7 chloroquinoline) like chloroquine is active against amebae in the tissues especially the liver when administered orally As in the case of emetine and chloroquine other amebicides should be used to supplement Camoquin to eliminate intestinal amebiasis

4 EMETINE *Emetine hydrochloride* has been the single most valuable drug for the treatment of amebiasis even though when given alone it will eliminate infection from the intestine in only a small percentage of cases Emetine affords prompt relief of symptoms in acute amebic dysentery and is the most potent therapeutic for hepatic and other forms of extraintestinal amebiasis The greater concentration and duration of emetine in the liver than in the intestinal wall are consonant with its high efficacy for hepatic amebiasis and its low parasitic cure rate for intestinal amebic infection

Emetine is a general protoplasmic poison which is eliminated from the body slowly and consequently it may produce cumulative effects In overdosage it produces focal necrosis of cardiac muscle and may cause cardiac failure and sudden death Even with a dosage that is generally considered safe toxic effects on the myocardium are frequently demonstrable during a standard treatment course The toxic manifestations are elevation of pulse rate fall of systolic blood pressure and electrocardiographic changes including depression or inversion of the "T" waves These changes in the electrocardiogram are reversible

Emetine should not be used in patients with myocardial disease or marked hypertension Owing to its toxicity it should not be used in ambulatory patients The use of emetine in children except under unusual circumstances is not advised It should not be administered during pregnancy unless absolutely necessary Because of the cumulative action of emetine when repetition of therapy is indicated at least two weeks should elapse before further administration of the drug

Emetine is prepared as a hydrochloride for parenteral injection It should always be given intramuscularly When administered subcutaneously it is extremely irritating and produces painful indurations which may persist for considerable periods It should never be given intravenously

Emetine Bismuth Iodide (*E B I*) This amebicide is a mixture of 29 per cent emetine 12 per cent bismuth and 58 per cent iodine In many areas of the world E B I is used extensively in the treatment of amebiasis Nausea vomiting and diarrhea may occur early in treatment The drug is given once daily and the patient should remain in bed Some recommend a sedative and tincture of opium to prevent vomiting and diarrhea

5 BISPHENOL *Biallylamicol hydrochloride* (Camoform) is a basic bisphenol which contains neither iodine nor arsenic The chemical designation of this synthetic phenol amebicide is diallyl diethylaminoethyl

phenol dihydrochloride It is active against dysenteric and nondysenteric amebiasis and may have some usefulness in extraintestinal amebiasis Side effects of Camoform include nausea vomiting anorexia abdominal distress and occasionally a maculopapular exanthem The drug should be discontinued in patients in whom skin rash occurs Camoform should not be confused with Camoquin

6 ANTIBIOTICS Many of the antibiotics have been studied to determine their potential value in the treatment of amebiasis A large number have shown some degree of therapeutic value for intestinal amebiasis The most efficacious are discussed below

Tetracyclines The broad spectrum antibiotics such as oxytetracycline and chlortetracycline have been found to be effective in the treatment of acute amebic dysentery as well as nondysenteric amebiasis Further pharmacologic studies of these two antibiotics have proved that the active principle in both is tetracycline The antibiotics are of little or no value in the treatment of extraintestinal amebiasis In acute amebic dysentery and in asymptomatic human infections oxytetracycline (Terramycin) when given alone in adequate dosage has been found to be better than 90 per cent effective in eliminating amebae from the tissues and contents of the intestine It produces a similar cure rate of mild or asymptomatic infections Tetracycline (Tetracyn, Achromycin) should afford equivalent results The mode of action of tetracyclines in intestinal amebiasis is primarily indirect since they affect the bacterial associates the presence or metabolites of which are essential to the amebae Antibiotics are useful for the treatment of selected cases of amebiasis particularly when dysentery is present and emetine is contraindicated or less desirable

Erythromycin (Erythrocin Ilotycin) will terminate diarrhea or dysentery and effect a high parasitic cure rate in intestinal amebiasis The drug in the form of erythromycin stearate is administered orally As in the case of other antibiotics it should not be relied upon for treatment of extraintestinal amebiasis

Fumagillin (Fumidil) is derived from *Aspergillus* sp and is an active amebicide in extremely high dilutions in vitro Unlike most antibiotics fumagillin acts directly against *E histolytica* Fumidil is an effective therapeutic for nondysenteric amebiasis but not for amebic dysentery or extraintestinal amebiasis Use of the drug may be associated with a papular rash on the hands and feet desquamation nausea diarrhea gas pains malaise furunculosis and on occasion by depression of leukocytes and platelets

Treatment for Nondysenteric Amebiasis Symptomless carriers and persons with occasional loose stools or other mild symptoms can be treated satisfactorily as ambulatory patients usually with either Milibis or Carbarsone followed by Diodoquin Frequently it may be desirable to supplement the intestinal amebicides concurrently with a course of Aralen Although the tetracycline antibiotics and erythromycin are effective against asymptomatic or mild clinical intestinal amebiasis their use in such cases ordinarily is not justified In children a course of Diodoquin without an arsenical or Aralen usually eliminates the infection and

is tolerated well Since amebicides are active directly or indirectly against the trophozoites their eradication results in the termination of the passage of cysts in the stool (see Table VI 6 p 287 for dosages)

Treatment for Amebic Dysentery The patient suffering from amebic dysentery or severe amebic diarrhea should be confined to bed although he may be given bathroom privileges The diet should be high in protein low in carbohydrate and supplemented by ample sources of vitamins especially of the B complex Although dehydration and toxemia are much less frequent and less severe than in acute bacillary dysentery adequate fluid balance must be maintained

Combined antiamebic therapy is essential In planning the details of the therapeutic program it is necessary to select a combination of drugs which will afford prompt relief of the dysentery and provide a parasitic cure Emetine hydrochloride ordinarily achieves the most prompt clinical alleviation of acute dysenteric amebiasis in adults Simultaneously it is active against any clinical or subclinical hepatic amebic involvement which may be present Since the parasitic cure rate of intestinal amebiasis with emetine alone is low it should be supplemented by effective intestinal amebicides

Oxytetracycline tetracycline and erythromycin have proved to be of value for the therapy of amebic dysentery in children or adults and are the drugs of choice for children These antibiotics produce a cessation of dysentery and achieve a high parasitic cure rate of intestinal amebic infection However they lack significant therapeutic value against hepatic amebiasis and should be supplemented by a 4 aminoquinoline Two regimens employing some of the above drugs for the treatment of amebic dysentery are outlined below

1 Emetine hydrochloride may be given intramuscularly to adults for a few days until the dysentery has been controlled then a course of Milibis (or Carbarsone) followed by Diodoquin is prescribed Aralen should be given concurrently with the intestinal amebicides since only a small quantity of emetine is employed in this regimen

2 Terramycin or Achromycin may be used for children or adults with amebic dysentery A course of Aralen should supplement these antibiotics

Numerous other combinations of amebicides have given effective results The daily doses of the various drugs are listed in Table VI 6 p 287

In severe cases which are associated with extensive secondary bacterial infection of the colon wall eradication of *E histolytica* may not be followed by cessation of symptoms The stools may continue to be loose and to contain pus mucus and blood In such instances antiamebic therapy should be followed by intensive antibacterial treatment until symptoms are controlled and microscopic pus and blood are no longer present in the feces

As a general rule if a patient has been treated two or more times for any form of intestinal amebiasis and laboratory reports still indicate *E histolytica* is present the validity of the laboratory findings should be questioned Similarly if clinical findings or complaints remain or recur

after two courses of treatment with amebicides, the diagnosis should be reconsidered and another sought

Table VI 6. Summary of Treatment of Amebiasis

DRUG	PRIMARY CLINICAL USAGE	RECOMMENDED DAILY ADULT DOSAGE	DURATION OF THERAPY IN DAYS
1 *Arsenicals*			
Carbarsone	Nondysenteric intestinal	0 25 gm b i d	10
Milibis	Nondysenteric intestinal	0 50 gm t i d	7
2 *Halogenated hydroxyquinolines*			
Diodoquin	Nondysenteric intestinal	0 65 gm t i d	21
Vioform	Nondysenteric intestinal	0 25 gm q i d	10
Chiniofon	Nondysenteric intestinal	1 0 gm t i d	8 10
3 4 *Aminoquinolines*			
Chloroquine	Extraintestinal	a 0 5gm b i d b 0 5 gm q d	a 2 b 12 19
Amodiaquin (Camoquin)	Extraintestinal	0 60 gm t i d	10
4 *Emetine*			
Emetine hydrochloride	Dysenteric and extraintestinal	0 065 gm q d *	4 10**
Emetine bismuth iodide	Nondysenteric intestinal	0 20 gm q d	10–12
5 *Bisphenol*			
Camoform	Dysenteric and nondysenteric	0 50 gm t i d	5 7
6 *Antibiotics*	—		
Oxytetracycline			10
Tetracycline			10
Erythromycin			5 7
Fumagillin			10

* Daily dosage of emetine hydrochloride is 1 mgm kg total daily dosage not to exceed 0 065 gm (1 grain)

** Maximum duration of therapy with emetine hydrochloride is ten days total dosage for this period not to exceed 10 mgm /kg (0 65 gm or 10 grains)

Complications. Amebic hepatitis and abscess of the liver are grave complications of intestinal amebiasis They may occur relatively early in the course of the disease or only after a prolonged period of chronic and often clinically latent infection During World War II cases of amebic abscess of the liver occurred among British troops within a few months after their arrival in India or Burma In New Guinea hepatomegaly and liver tenderness were observed in 25 per cent of military personnel treated for dysentery of varying severity Hepatomegaly was reported in 18 per cent of cases of acute amebic dysentery of short duration among prisoners of war in Korea.

Hepatic involvement results from metastasis of the infection in the wall of the colon to the liver by the portal blood stream A history of dysentery or of symptoms suggestive of antecedent amebic disease can

be obtained in a large percentage but certainly not in all cases of hepatic infection

Amebic Hepatitis Amebic hepatitis may develop during an acute stage of the intestinal infection or during a remission Less commonly it occurs in the absence of definite history of intestinal amebic disease The clinical picture may be extremely variable In the mild and sub-acute forms slight enlargement of the liver with moderate tenderness on palpation may be the only significant signs On the other hand acute amebic hepatitis is characterized by severe pain in the hepatic region toxemia marked pyrexia and an enlarged and markedly tender liver The fever usually is irregularly remittent reaching 103° to 104° F and in severe cases may closely simulate the Charcot type of curve observed in suppurative cholangitis The marked variations in temperature often accompanied by chills and profuse sweats may suggest malaria

There is diffuse but variable enlargement of the liver Palpation and even light percussion over the lower ribs may produce extreme pain The white blood count is moderately elevated with a polymorphonuclear leukocytosis of 70 to 80 per cent

DIAGNOSIS The diagnosis must be based primarily on clinical evidence A history suggestive of antecedent intestinal amebiasis or demonstration of *E histolytica* in the patient s stools together with remittent fever leukocytosis and right upper quadrant pain associated with enlargement and tenderness of the liver should immediately arouse suspicion Definitive diagnosis however depends upon the response to the therapeutic test with full dosage of emetine hydrochloride or chloroquine diphosphate Diagnostic aspiration of the liver should not be attempted in amebic hepatitis without definite evidence of large abscess formation Amebic hepatitis may be confused with malaria suppurative cholangitis or suppurative cholecystitis

TREATMENT Emetine hydrochloride and chloroquine have a specific amebicidal action against amebae within the tissues of the host The temperature pain tenderness enlargement of the liver and leukocytosis all show marked diminution within 48 to 72 hours after the initiation of specific therapy Treatment should consist of emetine hydrochloride by intramuscular injection daily for ten days or chloroquine diphosphate by mouth for 21 days (see Table VI 6 p 287 for dosages)

t

employed in place of the latter two intestinal amebicides

Amebic Abscess of the Liver Amebic abscess of the liver is commonly a late complication of amebiasis occasionally however it may develop within a relatively few months after the initial infection In some cases there is concurrent dysentery or a history of it Conversely many patients with amebic liver abscess give no history of diarrhea or dysentery The great majority of amebic abscesses of the liver occur in the right lobe approximately 16 per cent are in the left lobe In about 70 per cent of cases the cavity is large and single whereas in approximately 30 per cent two to four abscesses are present (Fig VI 17)

The clinical picture of acute amebic abscess is exceedingly difficult to distinguish from that of acute amebic hepatitis, particularly if the abscesses are multiple and involve both the right and left lobes Under such conditions the clinical phenomena will closely, if not exactly, resemble those of hepatitis without abscess and radiologic and physical findings are most important The response to specific therapy provides the most satisfactory means of differential diagnosis and is justified after a careful differential diagnosis has ruled out other possible causes

Chronic abscess is more commonly observed in the right lobe than in the left The symptoms are very variable, depending upon the size of the lesion, its situation with relation to other structures and the activity of the infection In many instances there is a history of gradual and progressive weight loss extending over a considerable time, with or without periods of low grade fever Variable and irregular pain referred to the right upper quadrant is often present, and a variety of digestive complaints which may arouse suspicion of chronic cholecystitis or even appendicitis are usual Right lobe abscesses commonly extend upward to involve the diaphragm In such cases irritation of the basal pleura frequently causes unproductive cough and pain on respiration Pain referred to the right shoulder is a frequent complaint

With further involvement of the pleura there may be signs of consolidation in the right lower lobe, with or without pleural effusion, leading to an erroneous diagnosis of pneumonia, empyema or tuberculosis If the process remains unrecognized spontaneous rupture into the right lower lobe with evacuation of the abscess contents through the bronchial tree may occur Occasionally the abscess may rupture into the abdominal wall

DIAGNOSIS Careful physical examination of the patient suffering from large single abscess of the liver should immediately arouse suspicion of the true nature of the lesion Enlargement of the liver is asymmetric The edge of the right lobe is usually easily palpable, and palpa



Figure VI 17 Amebic abscess of liver

tion typically elicits deep pain If the process is in the left lobe that portion of the liver is similarly affected When the abscess is on the right the diaphragm is commonly elevated and its mobility is impaired this may be demonstrable on physical examination as well as by roentgen examination and fluoroscopy Heavy percussion of the chest wall in the region of an abscess elicits deep pain As peripheral extension occurs toward the capsule of the liver a small area of intercostal tenderness may be noted When present it is the site of election for diagnostic aspiration

The white blood count usually is elevated moderately with an increased percentage of polymorphonuclear leukocytes

In those instances when it is impossible accurately to differentiate between acute abscess and hepatitis the therapeutic test with chloroquine or emetine should invariably be performed before attempting aspiration Diagnostic aspiration of the left lobe should never be attempted

For aspiration of the right lobe a large caliber needle attached to a syringe should be used and equipped with a stop so that the point cannot be introduced for a distance greater than 2½ inches from the skin In the absence of finger point intercostal tenderness the site of choice is in the anterior axillary line in the ninth interspace After Novocain anesthesia of the skin and deep infiltration the aspiration needle should be introduced medially and cephalad

The contents of an amebic abscess of the liver are usually semifluid and chocolate brown in color although in old chronic abscesses they may be yellowish or even white Amebae may be scanty in the necrotic contents of the cavity and therefore difficult or impossible to demonstrate in the aspirate in many cases Addition of 10 units of streptodornase per ml of the tenacious pus and incubation at 37° C with repeated shaking followed by centrifugation facilitates detection of the trophozoites They are present however in enormous numbers in the advancing border of the abscess wall (Fig VI 18) The contents of such an abscess are usually bacteriologically sterile but on occasion culture may reveal slight growth of avirulent bacteria Attempts to culture amebae from the sterile abscess contents invariably fail unless bacteria which will support the growth of *E histolytica* trophozoites in vitro are used The addition of *Clostridium welchii* or of other compatible bacteria or bacterial complexes obtained by separation from stock cultures of *E histolytica* to the cultures when they are inoculated with the abscess material frequently results in successful cultivation of amebae from liver abscess aspirates

Differential diagnosis is frequently difficult An acute abscess may be confused with acute hepatitis acute cholecystitis subphrenic abscess and malaria In the presence of chronic liver abscess the clinical picture may simulate carcinoma of the liver cirrhosis of the liver pleurisy with effusion atypical pulmonary tuberculosis arthritis of the cervical spine or shoulder and chronic cholecystitis or appendicitis

TREATMENT The high mortality previously associated with abscess of the liver was in large part due to the universal use of open drainage and the great difficulty in preventing secondary infection Although

open drainage is not recommended for right lobe abscesses, obviously it no longer would result in such a high mortality rate because of the introduction of antibiotics With the advent of emetine and the use of closed aspiration of the cavity, the mortality has been reduced to 2 per cent

liver pain and tenderness If there is no prompt clinical response after the institution of emetine therapy, the contents of the abscess cavity should be emptied as completely as possible by closed drainage and treatment with one of the antibiotics instituted at the same time In patients with large abscesses fever, pain and leukocytosis may recur or increase a few days after the primary aspiration This constitutes an imperative indication for further drainage of the cavity It does not necessarily indicate failure of specific therapy Such repeated closed drainage should be continued as indications require Laparotomy is required for drainage of a left lobe abscess because of the proximity of the pericardium

Intestinal amebicides should be employed to eradicate the source of the hepatic abscess A course of Milibis followed by Diodoquin or equivalent arsenical and hydroxyquinoline amebicides should be initiated as soon as practicable during emetine or chloroquine therapy Many physicians prefer to employ full courses of both emetine and chloroquine for the treatment of amebic liver abscess

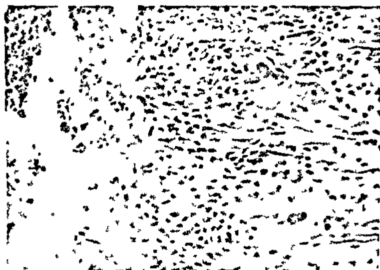


Figure VI.18 Trophozoites in wall of amebic liver abscess Necrotic abscess contents visible at extreme left. (Courtesy of The Louisiana State University School of Medicine)

Dientamoeba Diarrhea

Synonyms. None
Distribution. Worldwide
Clinical Characteristics. *Dientamoeba fragilis* has been considered to be a cause of chronic though mild intestinal symptoms There is controversy, however, concerning its actual pathogenicity Its ability to invade the tissues of the host has not been demonstrated The syndrome commonly ascribed to this organism consists of recurring episodes of lower abdominal discomfort and flatulence associated with the evacuation of two or three loose 'mushy' stools each day There is no mucus, blood or inflammatory exudate in the feces
Diagnosis. Microscopic examination of a fresh loose stool will reveal the trophozoites with characteristic spherical shape and some with extended pseudopodia (p 264) Red cells are not ingested, and no encysted stage is known *Dientamoeba fragilis* may be isolated in culture (p 820)
Treatment. The infection usually may be eliminated by one course of Carbarsone, Milibis or Diodoquin

Giardiasis

Synonyms. None
Distribution. Worldwide
Etiology. *Giardia lamblia* has been recovered from the duodenum and occasionally from the gallbladder It has been associated with symptoms referable to the duodenum This flagellate is not a tissue invader
Clinical Characteristics. Frequently, infections with *G lamblia* may cause no symptoms However, in a small percentage of cases of giardiasis epigastric discomfort, nausea and flatulence may be present Occasionally, in heavy infections, diarrhea may occur The stools in some cases are light colored and contain excessive amounts of fat The infection is more common in children than in adults, but symptomatic infection may occur in either age group *G lamblia does not cause dysen*tery or biliary tract disease In view of the simplicity and effectiveness of therapy for giardiasis, treatment of patients with this infection seems warranted and desirable
Diagnosis. The cystic stage is observed far more frequently than the trophozoite in stools Actively motile trophozoites occur in some diarrheal stools and may be present in large numbers in duodenal drainage fluid The detailed morphology is described on page 264 Attempts to culture this flagellate have not been successful

Treatment. Atabrine is a highly effective drug against *G lamblia* It should be given by mouth after meals for five days The individual dosage is 0 05 gram twice daily for children one to four years of age, 0 1 gram twice daily for those four to eight, and 0 1 gram three times a day for persons over eight years Only occasionally is a second course required to eliminate the infection

Trichomonas Vaginalis Infection

Synonyms. None

Distribution. Worldwide

Etiology. *Trichomonas vaginalis* is a flagellate often associated with a specific vaginitis or urethritis Infection becomes established when the acidity of the vaginal secretions is reduced *T vaginalis* will not survive at the normal vaginal acidity of pH 3 8 to 4 4 which is maintained by the conversion of glycogen in the epithelium to lactic acid by the normal bacterial flora and, indirectly by activity of the sex hormones

Coitus plays an important role in transmission The possibility of transmission of trichomoniasis by common use of douche equipment, clothing and towels in families or by contaminated instruments used for examination of patients should not be excluded in some cases Vaginal trichomoniasis is not acquired from the intestine by fecal contamination *T vaginalis* and *T hominis* are distinct species which are not interchangeable in their location in the body

Clinical Characteristics. Trichomonas vaginitis is accompanied by vulval pruritus, often intense, and a more or less profuse and irritating vaginal discharge which, in untreated cases, may lead to actual excoriation of the vulva and dermatitis of the adjacent skin of the thighs The vaginal mucosa is usually diffusely congested and inflamed A chronic urethritis may be seen in men

Diagnosis. Although *T vaginalis* at times may be detected in the urine of both women and men, vaginal and urethral secretion and prostatic fluid are the best diagnostic sources for demonstration of the flagellates The detailed morphology of *T vaginalis* is described on page 267 It may be isolated in culture (p 823)

Treatment. Successful treatment of trichomonas vaginitis is difficult and time consuming and requires persistence and complete cooperation by the patient The basic principles are cleanliness, restoration of normal vaginal epithelium and secretions, and destruction of the trichomonads by chemotherapeutic agents Patients who have passed the menopause may require estrogen therapy, and lesions of the cervix must be corrected

Various chemotherapeutic agents, including arsenicals sulfonamides antibiotics, and oxyquinoline derivatives used locally in the form of powders vaginal tablets and jellies have been recommended They are used in conjunction with measures for maintaining vaginal acidity Treatment of vaginal trichomoniasis is not always successful Local application of trichomonicides may fail to reach sites of residual infection such as glands and ducts An infected man may reinfect his coital partner Oral or systemic drugs for vaginal trichomoniasis such as Tritheon have yielded only limited success Aureomycin and Tritheon have shown significant effectiveness in eliminating trichomoniasis in men

A compound containing diiodohydroxyquinoline dextrose lactose and boric acid (Floraquin) has given good results It is recommended that two vaginal tablets be inserted into the fornices daily or that 4 to 8 grams of the powder be insufflated into the vagina three or more times a week Treatment should be continued until three monthly vaginal smears are negative

Balantidiasis

Synonyms Balantidial dysentery
Distribution Worldwide
Etiology. *Balantidium coli* is a pathogenic ciliate which occasion



Figure VI 19 *B coli* entering mucosa between basement membrane and epithelium.

ally infects the colon of man and may produce diarrhea and dysentery (Fig VI 19)

Pathology *Balantidium coli* penetrates the mucosa producing necrosis and ulceration There is no leukocytic infiltration until secondary bacterial infection occurs Occasionally masses of balantidia are found in the submucosa in a collagenous stroma without an accompanying inflammatory reaction (Fig VI 20)

As the ciliates invade the mucosa secondary infection rapidly occurs Superficial erosions are produced which extend laterally and penetrate into the deeper layers of the intestinal wall These are often hemorrhagic and in their gross appearance resemble the "Dyak hair" ulcers of amebic dysentery The lesions are discrete and the intervening mucosa is normal (Fig VI 21)

Clinical Characteristics Balantidiasis may be asymptomatic or may be associated with diarrhea or dysentery

Diagnosis Diagnosis depends upon demonstration of *B coli* in the feces The motile trophozoites will be found when the stools are liquid or semiliquid the cysts are seen in semiformed or formed stools The trophozoite is the more important diagnostic stage since it is observed in most if not all of the clinical cases of balantidiasis the cysts are seen only infrequently The detailed morphology of the ciliate is described on page 268 It may be isolated in culture (p 824)

Treatment Several of the antiamebic drugs are effective therapeutics for balantidiasis Favorable results have been obtained with Carbarsone Diodoquin Terramycin and Aureomycin A suitable regi



Figure VI.20 Chronic balantidial dysentery *B coli* in submucosa Inflammation and fibrosis.



Figure VI 21 Balantidial dysentery Ulcerations of colon with intervening normal mucosa

men consists of a course of Carbarsone followed by one of Diodoquin An alternate method of treatment is the use of Terramycin alone The dosage and duration of treatment with the above drugs are the same as employed for amebiasis (see Table VI 6 p 287)

Isosporiasis

Synonyms None

Distribution Widely distributed especially in the southwest Pacific and Philippines Infection has been reported from man also in *southern Europe the Middle East Africa Japan Vietnam Manchuria* South Central and North America and parts of the West Indies

Etiology *I belli* and *I hominis* are mildly pathogenic coccidial parasites of the small intestine of man

Clinical Characteristics and Pathology The infection in some instances is asymptomatic However diarrhea fever abdominal pain and tenderness flatulence nausea anorexia and headache may result from infection with these coccidia Although no lesions have been demonstrated at autopsy it is believed that transient microscopic lesions must be produced in the epithelial cells Infections are self limited In experimental infections in man symptoms developed in a week oocysts were recovered 9 to 15 days after ingestion and persisted for less than a month

Diagnosis Diagnosis depends upon demonstrating the unstained oocysts in the stool (see p 269) Oocysts of *I belli* have been found in duodenal drainage fluid

Treatment None as the infection is self limited

Prophylaxis Against Intestinal Protozoal Infections

Infection by the intestinal protozoa does not produce a protective immunity and artificial immunization has not been accomplished in humans Prophylaxis therefore depends upon avoidance of infection These organisms reach man through water or food polluted by human feces and foods contaminated by the droppings and vomitus of flies or by the soiled hands of infected foodhandlers Ice may be a vehicle of infection and should not be used in beverages or placed in contact with food in areas where it may be contaminated In heavily endemic areas all water for human consumption should be chemically treated or preferably boiled before use Raw vegetables must be scrupulously avoided and fruits should be scalded before consumption The exposure of fresh vegetables to acetic acid or vinegar for a minimum of 15 minutes would provide considerable but not necessarily complete protection against any *E histolytica* cysts present on the foods Whenever practicable foodhandlers should be examined and treated if infected Latrines must be fly proofed and kitchens and dining rooms adequately screened

35

Malaria

Revised by Martin D Young

Synonyms The synonyms of malaria in general are ague jungle fever paludism Synonyms of malaria due to *Plasmodium vivax* Benign tertian vivax malaria Synonyms of malaria due to *Plasmodium falciparum* Malignant tertian subtertian estivo autumnal E A *falciparum* malaria Malaria due to *Plasmodium malariae* is designated quartan malaria or *malariae* malaria Malaria due to *Plasmodium ovale* is designated *ovale* malaria

Definition Malaria is an acute and chronic infection characterized by fever anemia splenomegaly and often serious or fatal complications It is caused by protozoa of the genus *Plasmodium* Four species are pathogenic for man—*P vivax* *P falciparum* *P malariae* and *P ovale*

Distribution Malarial infections are prevalent between 45° north



Figure VI 24 Fresh unstained preparation showing oocysts on wall of mosquito s stomach



Figure VI 25 Various stages in development of oocysts—showing sporozoite formation and pigment masses (Courtesy Mr P G Shute F R E S Ministry of Health, Epsom England)

cell elongates and becomes motile, forming the ookinete or traveling vermicule This penetrates the wall of the mosquito's stomach, finally lodging beneath the outer layer.

It then undergoes progressive vacuolization to form a growing oocyst (Fig VI 24) The nuclear chromatin subdivides repeatedly, its particles becoming arranged along cytoplasmic strands bordering the vacuoles From each particle of chromatin in the protoplasmic mesh a filamentous structure extends into the lumen of a vacuole The chromatin particles become incorporated in these filaments to form sporozoites At maturity

the oocyst consists of a spongelike spherical body that projects into the body cavity of the insect In a suitable infected vector several hundred oocysts may be found on the stomach wall although as a rule they are scarce (Fig VI 25)

Spontaneous rupture of the oocyst finally occurs (Fig VI 27) Liberated motile sporozoites which may number several hundred to several hundred thousand migrate throughout the body cavity of the mosquito certain ones reaching and entering the salivary glands Here they lose their motility and remain dormant until injected into man (Figs VI 26 VI 28)

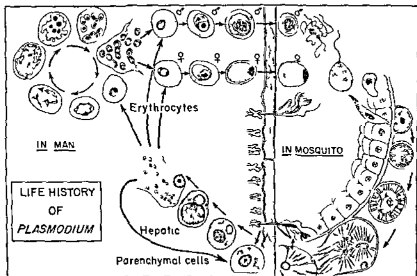


Figure VI 26 Life history of *Plasmodium* (Adapted from Wilcox Manual for the Microscopical Diagnosis of Malaria in the Man National Institutes of Health U S P H S Bulletin 180)



Figure VI.27 Empty capsule of oocyst after rupture and release of sporozoites



Figure VI 28 Sporozoites in salivary gland of mosquito and in surrounding fluid

The duration of the exogenous phase of the cycle, termed the extrinsic incubation period, varies with the species of *Plasmodium*, with the vectors, and with conditions of temperature and humidity Under favorable conditions, *P vivax* and *P falciparum* complete their development in the mosquito within seven to 14 days, *P ovale* requires several days longer and *P malariae* may require three weeks or more

The *endogenous* or *human phase* of the cycle begins with the injection of sporozoites by an infected anopheline mosquito The sporozoites disappear from the peripheral blood after about a half hour initiating the exo erythrocytic stage The parasites next appear in the parenchymal cells of the liver

The *P falciparum* parasites are 15μ in diameter by the third day after inoculation, contain 40 or more nuclei, and small vacuoles may be present (*Fig VI 36*) *As the parasite grows, there is a gradual increase in the* number of nuclei, cords or islands of cytoplasm appear from which the merozoites are formed After about six days the parasite is mature, is irregular in shape with lobes or projections, is about 60μ in longest diameter and produces about 40,000 merozoites The release of the merozoites from the mature schizont coincides with the appearance of ring stages in the erythrocytes of the peripheral blood This primary development constitutes the pre erythrocytic stage of the endogenous cycle

The rate of development and some of the morphologic characteristics vary with the species of parasites *P vivax* has a cycle length of eight days, with a mature schizont that is round, 45μ in size, and which contains 10,000 merozoites, *P ovale* requires nine days for development, has an irregular multilobular mature schizont about 80μ x 50μ, and produces 15,000 merozoites, *P malariae* requires over 11 days for the cycle and so far only the intermediate stages of the schizont have been described

The pre erythrocytic parasites do not contain pigment Except for the destruction of the parasitized parenchymal cells there is little evidence of injury to the liver

In relapsing malarias such as *P vivax* and *P malariae* the evidence indicates that the exo erythrocytic parasites persist in the liver parenchymal cells After a latent period merozoites are produced which invade

substance is bright red Pigment produced by the parasite in its growth appears as brownish or blackish granules The earliest form seen in erythrocytes consists of a small ring of blue stained cytoplasm with one or two dots of chromatin giving rise to the descriptive term "signet ring In the course of a few hours the ring develops into an actively motile ameboid form the trophozoite This term is applied to all the more mature intermediate stages in which the chromatin still appears as a single mass Later in development the chromatin undergoes repeated division Stages which exhibit cleavage of the chromatin without segmentation of the cytoplasm are referred to as presegmenting schizonts When division of both the chromatin and cytoplasm has been completed the form is termed a mature schizont each member of the resulting new generation of parasites being called a merozoite

Gametocytes are less numerous than asexual forms and therefore do not become readily apparent during the first schizogonic generations of *vivax ovale* and *malariae* infections In *falciparum* infections gametocytes appear about the tenth day of parasite patency In *vivax ovale* and *malariae* infections all forms from the early ring to the mature schizont and gametocyte are found in the peripheral blood In *falciparum* infections on the other hand only rings and gametocytes are usually demonstrable The intermediate development of this species occurs in the capillaries of the viscera and the intermediate stages are seen in the peripheral blood only infrequently and are usually associated with heavy infections

Plasmodium vivax The young plasmodia appear in stained blood films as delicate rings of blue cytoplasm each with a red bead of chromatin the so-called "signet ring They are approximately one third the diameter of a normal red blood cell The chromatin dots are usually but not invariably single and ordinarily not more than one parasite is observed within a single red cell The ring undergoes rapid growth and development the cytoplasm becomes heavier and thicker and the chromatin mass enlarges Within five or six hours yellowish brown pigment granules appear within the substance of the parasite which now develops into an actively motile trophozoite with bizarre outlines in the stained film The infected red cell gradually becomes swollen it stains less deeply and may present a diffuse bright red stippling the Schuffner s dots this stippling is not present in all cases When the parasite fills or nearly fills a considerably enlarged and pale red cell motility ceases and the chromatin undergoes successive divisions into 12 to 24 fragments with

an average of 16 The cytoplasm then undergoes similar subdivision each portion including one of the chromatin masses This mature schizont contains the new generation of asexual parasites, called merozoites and also the pigment formed during the period of growth clumped into one or two loose masses (Figs VI 29, VI 30) The length of the asexual cycle varies from 42 to 47 hours, depending upon the strain of *P vivax*

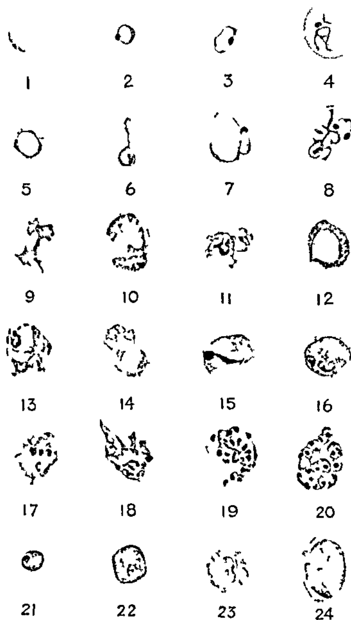
The mature male gametocyte is often about the size of a normal red cell and lies within an enlarged decolorized erythrocyte, its cytoplasm stains a light grayish or pinkish blue and the chromatin appears as granules loosely aggregated in the center or distributed as a transverse band The pigment is darker than in the schizont and is uniformly distributed The female gametocyte may be almost twice the size of a normal erythrocyte, its cytoplasm takes a deep blue stain, and the chromatin is compact usually situated near the periphery

Plasmodium falciparum The young rings are smaller and more delicate than those of *P vivax*, they are often hairlike and may show single or double chromatin dots Multiple infection of erythrocytes is common The frequently seen accole or applique form appears as a fine blue line with a delicate chromatin dot, apparently applied to the margin of a red cell *Plasmodium falciparum* remains in the ring stage longer than most species of *Plasmodium* The rings increase only slightly in size and remain smaller and more delicate After a few hours ring forms disappear from the peripheral circulation to undergo further development in the capillaries of the viscera There, intermediate and mature forms appear as small masses of light stained cytoplasm containing a chromatin granule, which is only slightly larger than that of the ring and a small round mass or block of black pigment Unlike *P vivax* and *P malariae*, which have diffuse pigment that forms an aggregate late in schizogony, the pigment of *P falciparum* appears as a solid block in the young trophozoite shortly after the ring stage The mature stages of the parasite are only about two thirds the size of a normal red blood cell (Figs VI 31, VI 32)

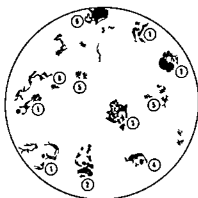
Parasitized cells of the peripheral blood may show cleftlike or commalike red markings, Maurer's dots These are larger and less numerous than the Schuffner s dots The infected red blood cells are not enlarged

---

Figure VI 29 *Plasmodium vivax* 1 Normal sized red cell with marginal ring form trophozoite 2 Young signet ring form trophozoite in a macrocyte 3 Slightly older ring form trophozoite in red cell showing basophilic stippling 4 Polychromatophilic red cell containing young tertian parasite with pseudopodia 5 Ring form trophozoite showing pigment in cytoplasm in an enlarged cell containing Schuffner s stippling (Schuffner s stippling does not appear in all cells containing the growing and older forms of *P vivax* as would be indicated by these pictures but it can be found with any stage from the fairly young ring form onward) 6 7 Very tenuous medium trophozoite forms 8 Three ameboid trophozoites with fused cytoplasm 9 11 12 13 Older ameboid trophozoites in process of development 10 Two ameboid trophozoites in one cell 14 Mature trophozoite 15 Mature trophozoite with chromatin apparently in process of division 16 17 18 19 Schizonts showing progressive steps in division (presegmenting schizonts) 20 Mature schizont 21 22 Developing gametocytes 23 Mature microgametocyte 24 Mature macrogametocyte (Courtesy National Institutes of Health U S P H S)



F gu e VI.29



1 Ameboid tropl ozoites
2 Schizont—2 divisions of chromatin
3 Mature schizont
4 Microgametocyte
5 Blood platelets
6 Nucleus of neutrophil
7 Eosinophil
8 Blood platelet associated with ce
remains of young erythrocytes

Figure VI 30 Plasmodium vivax in thick smear (Courtesy National Institutes
USPHS)

or decolorized The time required by *P falciparum* for completion of one generation of schizogony is considered to be about 48 hours From eight to 24 merozoites are formed

The gametocytes are elongated usually curved sausage-shaped bodies The male or microgametocyte stains lightly Its chromatin is loose and scattered and abundant granular brownish pigment is dispersed through the cytoplasm The female or macrogametocyte is often more slender longer and stains more deeply blue Its chromatin tends to appear as a compact mass in or near the center and the pigment is usually closely approximated to the chromatin The gametocytes or "crescents first

d subsequently recur in

malariae are about the size of those of *P vivax* Trophozoites are more compact less ameboid and tend to assume round or ovoid shapes Band forms are common the parasite extending as a band across the infected cell The pigment is darker brown coarser and appears in greater quantity and earlier than with *P vivax* The mature schizont fills or nearly fills an unenlarged and normally stained red cell Six to 12 merozoites are formed the usual number is eight These are arranged about the centrally collected pigment mass giving rise to a daisy head" or rosette appearance The asexual cycle requires 72 hours Gametocytes present the same differences between the sexes with respect to staining qualities and arrangement of chromatin granules as in *P vivax* (Figs VI 33 VI 34)

Plasmodium ovale This relatively uncommon species resembles *P vivax* in many respects Infected cells very early may show large numbers of coarse Schuffner's dots The growing trophozoites exhibit relatively little ameboid activity and consequently are more compact and more regular in outline than *P vivax* Band forms are noted frequently The mature schizonts form six to 12 merozoites with an average of eight The gametocytes resemble those of *P vivax* and are difficult to distinguish from them The infected red cells are less enlarged than in *P vivax* infections but are decolorized The margin of the infected cell is often crenated or fimbriated and the cell tends to be oval in shape (Fig VI 35) The asexual cycle lasts about 50 hours

Host Parasite Relationship Following injection of sporozoites by infected mosquitoes at the end of the extrinsic incubation period, the parasites develop in the liver parenchymal cells Upon the maturation of these pre erythrocytic stages merozoites are released which invade erythrocytes marking the end of the *prepatent period* For the detection of the parasites by ordinary microscopic examination of the thick blood smear a minimum of ten parasites per cubic millimeter of blood is normally required

The prepatent periods vary according to species the usual lengths being *P vivax* 12 to 14 days *P falciparum* ten to 13 *P ovale* 12 to 20 and *P malariae* 27 to 37 These periods may be shortened but not to less than five days by inoculations of larger numbers of sporozoites or lengthened by the injections of fewer sporozoites

The interval between the infective bite and the first elevation of tem

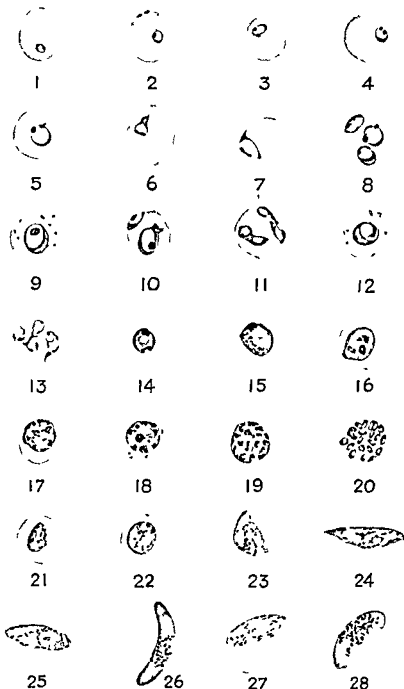


Figure VI 31 *Plasmodium falciparum* 1 Very young ring form trophozoite 2 Double infection of single cell with young trophozoites one a marginal form the other signet ring form 3 4 Young trophozoites showing double chromatin dots 5 6 7 Developing trophozoite forms 8 Three medium trophozoites in one cell 9 Trophozoite showing pig

perature to 100 F is termed the *intrinsic incubation period* It may coincide with the *prepatent period* rarely is shorter and more often is a day or two longer The febrile reaction is related to the sporulation of parasites The densities of the parasites at the first fever in a nonimmune person usually are between ten and 100 per cubic millimeter, but they may be below densities (10 per cubic millimeter) detectable by ordinary microscopic examination or especially in persons with high immunity may be in the thousands per cubic millimeter In general *P falciparum* has greater densities in all stages of the asexual cycle than do the other species

There are fundamental differences in the invasive characteristics of these three species of *Plasmodium* These differences are to a considerable extent responsible for the marked variations in severity of the disease produced by them

Plasmodium vivax attacks the reticulocytes almost exclusively and appears incapable of invading mature erythrocytes This imposes a limit on the magnitude of the parasitemia which usually ranges from 8000 to 20 000 per cubic millimeter and only rarely exceeds 50 000 per cubic millimeter

Plasmodium falciparum however invades all the red cells irrespective of age There is consequently no limiting factor to prevent progressively increasing parasitemia Very high densities may therefore be encountered in *falciparum* infections A parasitemia of 500 000 parasites per cubic millimeter carries a grave prognosis and even low parasite densities should be considered dangerous Unlike *P vivax* and *P malariae* *P falciparum* induces physical changes in the infected red blood cells which contribute importantly to the pathology of the infection The infected cells agglutinate forming thrombi and emboli They likewise adhere to the capillary endothelium These effects produce capillary obstruction and severe ischemia in many tissues of the body

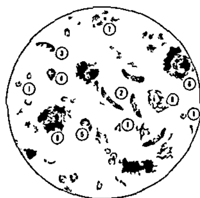
Plasmodium malariae attacks predominantly the mature erythrocytes Parasitemias exceeding 20 000 per cubic millimeter are uncommon After the acute primary attack the infection tends to become chronic often persisting for years in a patent or subpatent condition

Characteristics of P vivax Infections In the early stages of infection by *P vivax* usually two groups of parasites undergo schizogony concurrently maturing on alternate days This results in the release of a new generation of merozoites each day and a corresponding quotidian

---

ment in a cell containing Maurer s dots 10 11 Two trophozoites in each of two cells showing variation of forms which parasites may assume 12 Almost mature trophozoite showing haze of pigment throughout cytoplasm Maurer s dots in the cell 13 Estivo-autumnal slender forms 14 Mature trophozoite showing clumped pigment 15 Parasite in the

USPHS)



1 Small trophozoites
2 Gametocytes—normal
3 Slightly distorted gametocyte
4 Rounded up gametocyte
5 Disintegrated gametocyte
6 Nucleus of leukocyte
7 Blood platelets
8 Cellular remains of young erythrocyte

Figure VI 32 *Plasmodium falciparum*—thick film (Courtesy of National Institutes of Health U S P H S)

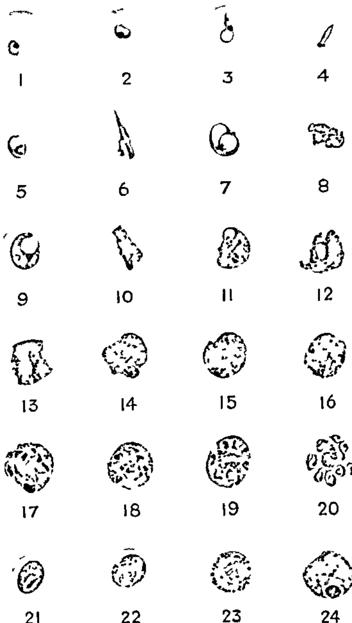
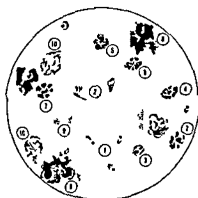


Figure VI.33 *Plasmodium malariae* 1 Young ring form trophozoite of quartan malaria 2 3 4 Young trophozoite forms of the parasite showing gradual increase of chromatin and cytoplasm 5 Developing ring form trophozoite showing pigment granule 6 Early band form trophozoite—elongated chromatin, some pigment apparent. 7 8 9 10 11 12 Some forms which the developing trophozoite of quartan may take 13 14 Mature trophozoites—one a band form. 15 16 17 18 19 Phases in the development of the schizont (presegmenting schizonts") 20 Mature schizont. 21 Immature microgametocyte 22 Immature macrogametocyte 23 Mature microgametocyte 24 Mature macrogametocyte (Courtesy National Institutes of Health, U.S P.H.S)



1 Small trophozoites
2 Growing trophozoites
3 Mature trophozoites
4 5 6 Schizonts (presegmenting) with varying numbers of divisions of the chromatin
7 Mature schizonts
8 Nucleus of leukocyte
9 Blood platelets
10 Cellular remains of young erythrocytes

Figure VI 34 *Plasmodium malariae* in thick smear (Courtesy National Institutes of Health USPHS)

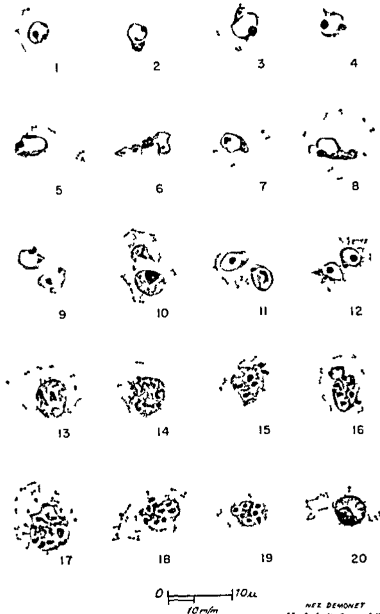


Figure VI-35. *Plasmodium ovale*. *1*, Young ring-shaped trophozoite. *2*, *3*, *4*, *5*, Older ring-shaped trophozoites. *6*, *7*, *8*, Older ameboid trophozoites. *9*, *11*, *12*, Doubly infected cells, trophozoites. *10*, Doubly infected cell, young gametocytes. *13*, First stage of the schizont. *14*, *15*, *16*, *17*, *18*, *19*, Schizonts, progressive stages. *20*, Mature gametocyte.

Free translation of legend accompanying original plate in "Guide pratique d'examen microscopique du sang appliqué au diagnostic du paludisme" by Georges Villain. Reproduced with permission from "Biologie Medicale" supplement 1935.

(Courtesy of Aimee Wilcox, National Institutes of Health Bulletin No. 180, U.S.P.H.S.)

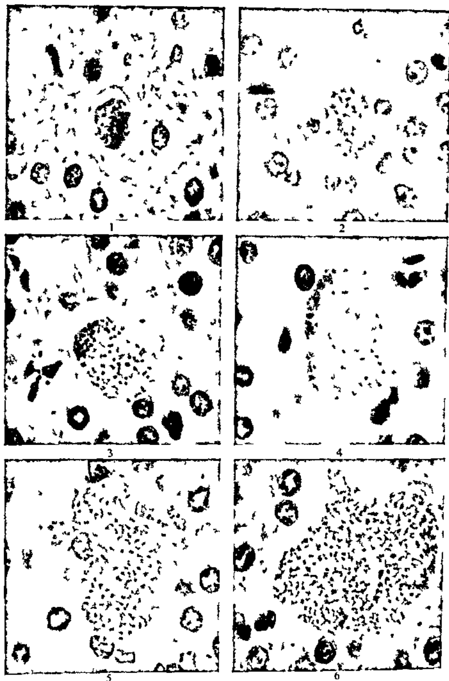


Figure VI 36

febrile reaction Gradually or suddenly one group may drop out Maturation of the parasites then occurs in from 42 to 47 hours and the accompanying febrile curve becomes characteristically tertian appearing progressively earlier every other day In an untreated case a second group ultimately may *reappear its members gradually increasing in numbers* as the others decrease and the fever again becomes quotidian The naturally evolving *vivax* infection therefore consists of a series of such alternating and overlapping groups with corresponding periods of tertian and quotidian fever The latter type of curve depends upon this phenomenon and not as has been said in the past upon double infection acquired on different days Gametocytes infective to mosquitoes appear in the peripheral blood within a few *days after the end of the prepatent* period

Characteristics of P falciparum Infections Infections by *P falciparum* differ in certain important respects from those by *P vivax* The period required for maturation of the parasites is approximately 48 hours and schizogony is less synchronized Release of the new generation of parasites is continued over a longer period As a result the febrile episodes are less regular and more prolonged in duration In severe infections the fever is frequently continuous

Gametocytes do not appear in the peripheral blood until about ten days after the onset of the primary parasitemia They become infective for mosquitoes about four days later In naturally evolving infections as the gametocyte count rises the trophozoite count diminishes and clinical improvement or remission of symptoms frequently occurs The primary parasitemia is *characterized by* such a series of successive trophozoite gametocyte waves Parasite counts in *falciparum* malaria characteristically fluctuate much more markedly than do those of *vivax* often showing alternating high and low densities on successive days

Characteristics of P malariae Infections In the early stages of infections by *P malariae* there is usually only one group of parasites

fore recur at intervals
two additional groups
even quotidian fever

Figure VI.36 Exo-erythrocytic Stages of *Plasmodium falciparum* in liver

1 This is one of the smallest parasites seen Diameter 15μ. Probably three days old.

2 A larger parasite than that shown in figure 1 Sections cut at two microns and stained with Delafield s hematoxylin.

3 A larger stage than that in preceding figures

4 A still larger stage with nuclei and cytoplasm more condensed on the left side Note that although sinusoids may be clearly seen on each side of the parasite the parasite is not in contact with these spaces

5 A parasite approaching maturity with vacuolization cutting the cytoplasm into cords and islands (Shortt s pseudocytomeres") Note the growth of the parasite around the unchanged nucleus of the hepatic epithelium.

6 A mature schizont. *Note the cords and islands in* the parasite and the formation of merozoites especially at the top of the parasite Diameter about 60μ. (Courtesy Jeffery Wolcott, Young Williams Am J Trop Med & Hyg 1 917 1952)

Characteristics of Mixed Infections When two species of malaria are present in the human host simultaneously, there appears to be a competitive antagonism between them If *P falciparum* and *P vivax* are both present the former predominates initially after which the *vivax runs its course* When *P vivax* and *P malariae* are together the *P vivax* is the dominant species initially sometimes to the complete expulsion of the *P malariae Plasmodium vivax* is even more dominant over *P ovale* when the two are together than over *P malariae*

The Primary Attack and Relapses Study of naturally induced mosquito transmitted *vivax* infection indicates that in wholly susceptible persons the patent primary parasitemia may persist for as long as three months In the course of this period however *there may be transitory* intervals when the parasite densities are depressed Such depressions are frequently accompanied by clinical remissions The duration of clinical symptoms is considerably shorter than the total period of primary parasitemia and it may be continuous or interrupted by one or more remissions Any clinical activity occurring within this period is considered part of the primary attack of malaria

Disappearance of the asexual parasites for several weeks either naturally or because of treatment marks the end of the primary attack The exo erythrocytic parasites persist in the parenchymal cells of the liver and it is believed that after a latent period these produce parasites which again invade the erythrocytes *causing relapses The intervals to* relapse after noncurative treatment vary In some *vivax* strains this interval may be nine to ten months in others several weeks In contrast to *vivax* infections the exo-erythrocytic forms of *falciparum* are short lived and do not persist in the liver

The natural duration of malaria infections varies Experimentally induced infections of a single *vivax* strain may persist for 12 or 18 months Some of the *vivax* strains acquired in the Pacific during World War II persisted for as long as four years *Plasmodium falciparum* experimental infections endure an average of seven to nine months with a small proportion lasting 17 months *Plasmodium malariae* may persist *for many years most of the time without a demonstrable parasitemia or clinical symptoms Plasmodium ovale* relapses only infrequently and only rarely persists longer than one year

Immunity The Negro race has a relative racial immunity against *P vivax* Experimental studies have indicated that infections by *P vivax* and *P falciparum* produce an homologous immunity This is strictly strain specific the individual becoming refractory to subsequent reinfection by the strain previously used He is not immune however to other strains of the same species although the severity of the infection produced by them is frequently modified There is no cross immunity between species thus infection by *P vivax* confers no immunity against *P falciparum* and the clinical disease produced by the latter is unmitigated in severity

The development of immunity is first characterized by the acquisition of *tolerance* to the infection This is expressed by cessation of clinical phenomena despite persistence of a parasitemia considerably *in excess*

of that which accompanied the onset of the initial clinical represents apparently a form of immunity depending upon latent infection Agglutinins precipitins and complement bodies are produced The defense mechanism however largely cellular in nature This immunity expressed as to premunition is of great importance in the epidemiology of m

Epidemiology Malaria has a higher morbidity rate an sible for more deaths per year than any other transmissi As recently as 1955 it was estimated that there were 250 r of malaria with 2 5 million deaths annually and that mor million people were exposed to malaria by living in malario The great importance of malaria as a military problem was demonstrated in World War I when in the course of c Macedonia the British French and German armies were by this disease In World War II it constituted the major military medicine throughout the tropical and subtropical t ticularly the Mediterranean India Burma China the Phil the south and southwest Pacific In the latter area malaria had effect upon the development and progress of military op this region also a peculiarly resistant strain of *P vivax* was which was characterized by repeated relapses over an un period More recently experience in Korea has demonstrated may be a problem for armies in the field even in the temper

The degree of endemicity or the level of transmission o any region is determined by a variety of interrelated factor important of these are

1 The prevalence of infection in man—the reservoir
2 The species of indigenous anopheline mosquitoes t abundance their feeding and resting behaviors and vidual suitability as hosts for plasmodia—the vector
3 The presence of a susceptible human population—the n
4 Local climatic conditions
5 Local geographic and hydrographic conditions whic anopheline breeding areas (Fig VI 37 Table VI 7)

It is apparent however that there must be other controllin for in areas in which the disease is endemic the incidence over long periods exhibits cyclic increases and recessions t which are not understood

In many parts of the world there is a definite annual flu usual sequence in the times of appearance of the different disease These are probably dependent upon seasonal variat perature humidity and rainfall affecting both the breeding o vectors and the development of the exogenous phase of t in them

The average climatic conditions in the temperate zone velopment and transmission of *P vivax* and *P malariae* favorable to *P falciparum* These factors together with rel

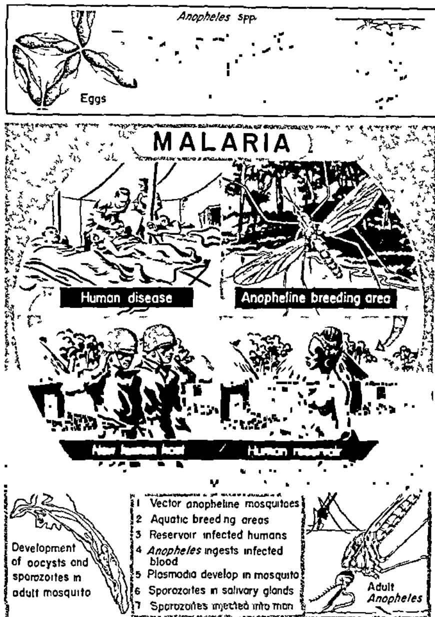


Figure VI 37 Epidemiology of malaria

P vivax infections are the earliest to appear in the spring whereas *P falciparum* and *P malariae* do not reach their peak until late summer and early autumn

In the true tropics rainfall is the determining factor controlling anopheline breeding In areas where there are wet and dry seasons each year there are commonly two peaks of incidence The first follows

shortly after the beginning of the rains The second and frequently the more important appears at the end of the rainy season when ample anopheline breeding areas are present and when the destructive action of heavy rainfall upon the larvae is diminished

In mountainous tropical countries both *P vivax* and *P falciparum* are prevalent in the hot moist lowlands At higher altitudes as the average temperatures more nearly approach those of temperate zones *P falciparum* gradually disappears *Plasmodium vivax* however may be heavily endemic in certain regions at altitudes even in excess of 8000 feet

Evaluation of the malaria problem in any area entails study of all the known factors which contribute to the endemicity and the transmission of the disease

Malaria reconnaissance provides a rapid superficial and statistically inexact estimate of the situation The data provided by such an investigation are insufficient for the preparation of a detailed control program

A *malaria survey* on the other hand is an intensive detailed often time consuming study of all relevant local factors It should be carried on throughout a year to secure accurate information adequate for planning a control program

Evaluation of Infection of the Human Reservoir Evaluation of the degree of infection of the human reservoir is based upon the following findings

1 SPLEEN RATE This is the per cent incidence of splenomegaly in children of the indigenous population two to nine years of age inclusive The age group may be varied in certain regions

2 ADULT SPLEEN RATE When the number of children is insufficient adults may be included in the figures The incidence of splenomegaly in the adult population is lower however and consequently the qualifying term "adult" must be included to avoid misinterpretation of the data

3 PARASITE RATE This is the per cent incidence of blood films showing malarial parasites in children of the indigenous population two to nine years of age inclusive

4 TRANSMISSION INDEX This is the per cent incidence of blood films showing malarial parasites in infants of the indigenous population under one year of age It provides important information concerning variations in the seasonal transmission rate of malaria in the particular area and is the best indication of the effectiveness of control measures

Certain arbitrary terms have been accepted to express the *intensity of infection* in a given area These are

1 Low endemicity—spleen rate under 10 per cent
2 Moderate endemicity—spleen rate 10 to 25 per cent
3 High endemicity—spleen rate 25 to 50 per cent
4 Hyperendemicity—spleen rate 50 per cent or over

The Insect Vector The definitive host of the plasmodia is the anopheline mosquito There are over 200 known species of anophelines of which only about 50 have been incriminated as vectors of malaria

Determination of the particular species which are or may be efficient vectors and estimation of their relative abundance in an area are essential

Table VI 7. Principal Vectors of Human Malaria (Cont'd)

REGION	AREA	SPECIES	TYPE OF BREEDING PLACE		ADULT BEHAVIOR	EFFICIENCY AS VECTOR
			LIGHT REQUIREMENTS	WATER, VEGETATION, ETC.		
Palaearctic (cont'd)	Spain, Italy, Balkans to southeast Asia	*A. superpictus*	Sun	Fresh water pools, streams, drains, seepages especially in hillsides	Prefers human blood, readily enters houses, tents, barracks; strong fliers	Important in Europe, Middle East, W. Pakistan
	Japan, North and Northeast China, Korea, South Ukraine					
	See Burma, etc., for China (not south of 30° N. lat.)	*A. hyrcanus sinensis* *A. pattoni*	Sun	Among algae along stream margins, rain pools, small pools of stream beds in hills	Bites man	Important vector
Ethiopian	Central and South Africa, Tropical Africa north to Ethiopia	*A. funestus funestus*	Partial shade	Clear water of swamps, weedy banks of streams, rivers, ditches, margins of lakes, ponds, underground seepages	Enters houses in large numbers, feeds freely on human blood, a few migrate up to 4½ miles	Always important (also carries filariasis)
	Tropical Africa, Arabia, Madagascar, Reunion, Mauritius, other points	*A. gambiae*	Sun or slight shade	Puddles, shallow ponds, borrow pits, hoofprints, ditches, overflows, rarely rain barrels, cisterns	Prefers human blood, abundant in huts and houses; a few migrate up to 3½ miles	Always important (also carries filariasis)
	Sierra Leone, Liberia, Cameroons, Uganda, Belgian Congo	*A. hancocki*	Sun to slight shade	Clear water in grassy holes, native wells, streams, swamps	Found commonly in human dwellings	Important where prevalent
	Sierra Leone, Liberia, S. Nigeria, Gaboon, Belgian Congo	*A. hargreavesi*	More or less shade	*Among Pistia in open jungle* swamps, stream margins (vegetation)	*Abundant in huts in Nigeria*; bites at midnight or later	*Important where common*
	Belgian Congo, Uganda, Cameroons	*A. moucheti moucheti*	Sun to slight shade	Among vegetation on margins of pools, streams, permanent swamps	Often found indoors	Rather important where common
	Southern Nigeria	*A. moucheti nigeriensis*	Sun largely	Clear water in swamps (*Pistia* and other vegetation)	Found in native huts	Rather important where common
	Sierra Leone, Liberia, Gold Coast, Nigeria, Cameroons—eastward to Mozambique	*A. nili*	Heavy shade	Among vegetation along sides of running streams	Common in huts and camps but rare in houses	Possibly important where prevalent
	Coastal West Africa	*A. melas*	Shade	Breeding associated with black mangrove trees (*Avicennia* sp.) in brackish water, coastal streams and tidal swamps	Feeds more on dark nights; most remain in huts after feeding	Important in some coastal areas of West Africa

Ethiopian (cont'd)	Many parts of Africa, Madagascar, Israel	*A. pharoensis*	Sun to partial shade	Swamps and rice fields; vegetation essential	Enters houses in large numbers, bites man readily but prefers animal blood	Important in upper Nile Province, Sudan; Fr. W. Africa
	F. Central and S. Africa, N. and S. Rhodesia, Sudan	*A. rufipes*	Sun	Pools, marshes, hoofmarks, artificial containers	Rests in crevices and outdoor haunts near breeding places; occasionally found in large numbers indoors	S. Rhodesia, Fr. W. Africa, Sudan; usually of secondary importance
Oriental	Afghanistan, Pakistan, India, Burma, Ceylon India, S. China, Formosa, entire Malay region and Philippines	*A. annularis* (= *fuliginosus*)	Sun to partial shade	Large tanks or fresh water ponds, slowly moving streams, lake margins (with aquatic vegetation)	Prefers cattle to man; flies great distances; occurs up to 7000 ft	Of secondary importance
	W. Pakistan to Burma, Ceylon, Thailand, Tonkin Prov., S. Arabia	*A. culicifacies*	Sun to partial shade	Wide variety of places; prefers fresh clean water in pools but can survive in brackish	Prefers cattle but bites man freely; rests in cow sheds and *houses during* day	Most important vector in India; only vector in Ceylon
	In foothills from W. Pakistan to Burma, South India, [illegible], Thailand, *Tonkin Prov.*	*A. fluviatilis* (= *listoni*)	Sun	Stream edges, stream pools, springs, irrigation channels, more rarely swamps, lakes	Prefers human to animal blood; found in houses, cow sheds	Important vector in rural foothills (1000-5000 ft)
	E. and S. India, Burma, Thailand, Vietnam, S. China, Formosa	*A. minimus*	Sun	Slow running streams, springs with grassy margins, irrigation ditches, rice fields, seepage areas	*Remains in houses* and cow sheds after feeding	Always important, especially so in India, Burma, Thailand, S. China up to 5,500 ft.
	India, Burma, *Malaya*, Thailand, Vietnam, Indonesia, Philippine Islands	*A. philippinensis*	Sun to partial shade	Pools, drains, ditches, tanks, swamps, borrow pits, rice field, grasscovered stagnant waters	Found in houses, stables, cattle sheds	Important in Bengal; probably not vector in Philippine Islands
	See Persian Gulf etc. for *India*, *Burma*, Thailand, Malaya, Sumatra, Java, Borneo, *Lesser* Sunda Islands, Celebes	*A. stephensi* *A. sundaicus*	Sun	Brackish or salt water in lagoons, *swamps and* behind coastal embankments	Prefers human blood (?); *found in large numbers in* cow sheds, houses; strong fliers	Important in Bengal, Malaya, Vietnam, Indonesia
	See Persian Gulf etc. for India, Burma	*A. superpictus* *A. varuna*	Sun or shade	Stagnant water of pools, *ditches, wells*, [illegible]	Feeds readily on man; found in houses, cow sheds	Proved vector in some localities
	India, Ceylon, Burma, Thailand, Cochin China, Malaya, Sumatra, Java, Borneo, Celebes	*A. aconitus*	Sun to partial shade	Irrigation ditches, swamps, ponds, rice fields, pools in creek beds, storm drains, *reservoirs with grassy* margins	Feeds readily on man and animals; found in houses, cow sheds (1200 to 2000 ft); strong fliers	Important in Vietnam
	See Afghanistan etc. for N. E. India, Burma, Vietnam, China, Korea, Japan, Formosa, Okinawa	*A. culicifacies* *A. hyrcanus sinensis*	Sun	Stagnant water in rice fields, pools, ponds, swamps, *rarely stream* or lake margins	Not recorded as domestic	Vector in S. Japan, Korea, Okinawa, Indonesia, and in China
	Malaya, Sumatra, Borneo, Java, Celebes	*A. hyrcanus* [illegible]	Same as for *A. hyrcanus sinensis*	Same as for *A. hyrcanus sinensis*	Same as for *A. hyrcanus sinensis*	Important vector in Java and Celebes

Table VI.7. Principal Vectors of Human Malaria (Cont'd)

REGION	AREA	SPECIES	TYPE OF BREEDING PLACE: LIGHT REQUIREMENTS	TYPE OF BREEDING PLACE: WATER, VEGETATION, ETC.	ADULT BEHAVIOR	EFFICIENCY AS VECTOR
Oriental (cont'd)	India, China, Tonkin Prov., Burma, Formosa	*A. jeyporiensis candidiensis*	Sun to slight shade	Running water in ditches	Not recorded as domestic	Vector in Tonkin Prov.
	India, Ceylon, Burma, S. China, Thailand, Malaya, Indonesia, Vietnam, Formosa, Philippines	*A. maculatus maculatus*	Sun to very slight shade	Stream and river beds, seepages, also pools, rice fields, lake margins, ditches	Enters houses temporarily, bites humans	Important in Malaya and Indonesia
	See Afghanistan, etc., for	*A. minimus*				
	See Afghanistan, etc., for	*A. sundaicus*				
	E. India, Tonkin Prov., Malaya, Cochin China, Sumatra, Java, Borneo, Celebes	*A. umbrosus*	Shade (can tolerate sunlight)	Stagnant jungle pools and morasses, brackish water in mangrove swamps	Fierce biter, found in dense forests, jungles, also in houses, strong flier	Important in some areas
	Philippine Islands and south to Java	*A. minimus flavirostris*	Sun and shade	Clear water of shaded streams (bamboo roots), rivers, irrigation ditches, pools, wells	Enters houses to attack man, leaves after feeding, rests under overhanging banks	The important vector in the Philippines
	Indonesia					
	See Burma, etc., for	*A. aconitus*				
	India, Ceylon, Burma, Thailand, Vietnam, China, Malaya, Sumatra, Borneo, Java, Lesser Sundas, Celebes, New Guinea, Philippines	*A. barbirostris barbirostris*	Sun and shade	Clear water of shaded streams, rivers, vegetated ponds, pools, flowing ditches, canals, borrow pits, rice fields, salt water swamps, wells	Hides by day (in shade), enters houses rarely, prefers blood of domestic animals	Of little importance (found infected in Malaya, Indonesia)
	India, Ceylon, Burma, Thailand, Vietnam, China, Malaya, Sumatra, Java, Celebes, Borneo, Philippines	*A. hyrcanus nigerrimus*	Sun largely	Rice fields especially stagnant, vegetated canals, borrow pits, lakes, impounded areas, slow streams	A wild species, invades houses rarely, feeds on man or animals	Of some importance in Malaya and Indonesia
	India, Ceylon, Burma, Vietnam, Malaya, Sumatra, Java, Borneo, Philippines	*A. leucosphyrus leucosphyrus*	Heavy shade required	Rock pools, stagnant pools in beds of mountain streams	A wild species found in dense jungles	Found infected in Indonesia
	See Burma, etc., for	*A. maculatus*				
	See Afghanistan, etc., for	*A. minimus*				
	India, Malaya, Indonesia, New Guinea	*A. subpictus subpictus*	Sun or shade	Fresh, brackish or contaminated pools, borrow pits, wallows, roof gutters, containers	Feeds on man, other animals, but prefers cattle, numerous in cow sheds, houses, barracks	Believed important in Celebes
	See Afghanistan, etc., for	*A. sundaicus*				
	See Burma, etc., for	*A. umbrosus*				
Australian	New Guinea, New Britain, Solomons, New Hebrides, Admiralties, N. Australia	*A. farauti* (= *punctulatus moluccensis* of authors)	Sun or slight shade	Fresh or brackish water, natural or artificial, clear or polluted	Bites freely both at night and in daytime shade, exclusively anthropophilic	Dominant carrier in this area
	New Guinea, Bismarck Archipelago and Solomon Islands	*A. punctulatus punctulatus*	Sun	Small rain pools, stream margins, rarely in larger bodies of water	Frequents houses, bites throughout night, strong flier	Important in New Guinea, probably also in Solomons

functions of the malaria survey The marked variation in the capacity among different species to transmit the disease depends upon certain [illegible]

exclusively on animal rather than human blood whereas others feed with equal frequency on blood from man or animals Some remain in or close to dwellings after obtaining a blood meal others immediately leave the human environment Similarly there are great variations in flight range Some anophelines are weak fliers and travel only short distances but the normal flight range of others may be several miles

Malaria tends to be a place disease with highest incidence close to important mosquito breeding areas and the location and description of such areas are therefore essential functions of the survey In general anopheline larvae require clear water with an adequate content of algae for optimal growth The typical habitats of different species vary greatly Some species seek only sunlit water others flourish in shade Certain ones cannot utilize water containing even small amounts of salt others thrive in brackish water containing 40 to 60 per cent sea water Some species utilize streams or seepage areas others only swamps and marshes Such variations in specific habitats form the basis for so called naturalistic control methods which are designed to alter the natural characteristics of a breeding area rendering it unsuitable for larval development

The final evaluation of the importance of a particular anopheline species as a vector of malaria is based upon certain specific procedures

1 EPIDEMIOLOGIC INDEX This expression represents the attempt to establish a significant correlation between the prevalence of a particular species of anopheline and the transmission of the disease It is seldom a practicable procedure and rarely affords dependable evidence

2 EXPERIMENTAL INDEX OF INFECTION Laboratory raised female anophelines of a given species are fed upon a human gametocyte carrier They are subsequently dissected and the percentage showing oocysts on the stomach wall and sporozoites in the salivary glands is noted This procedure may give accurate information of the biologic suitability of the particular anopheline to serve as a definitive host for the *Plasmodium* It does not provide information as to the importance of the species as a *natural* vector A number of species of no practical importance in the transmission of malaria may nevertheless yield a high index of experimental infection

3 NATURAL INDEX OF INFECTION Large numbers of captured anopheline mosquitoes are dissected and the per cent prevalence of oocyst formation on the stomach wall and of sporozoite infection in the salivary glands is noted The prevalence of salivary gland infection provides the more important information A salivary gland index as low as 0 1 per cent or even lower nevertheless indicates an important transmitter when the species is very abundant Much higher rates may be encountered exceptionally In the course of epidemic malaria in north

eastern Brazil the salivary gland infection rate of *Anopheles gambiae* reached 30 2 per cent (see pp 825–826)

4 THE PRECIPITIN TEST The precipitin test applied to the gut contents of engorged mosquitoes provides a means of distinguishing between anthropophilic and zoophilic species (p 835)

Pathology Malaria is accompanied by the destruction of enormous numbers of red blood cells both parasitized and nonparasitized and a consequent increase in the bilirubin content of the blood The hemolysis may be so intense in *P falciparum* infections as to cause hemoglobinuria and blackwater fever Severe grades of anemia may be produced and reticulocyte crisis may follow upon effective therapy In chronic cases however the anemia may be refractory At least three factors appear to contribute to this they are continued destruction of erythrocytes failure of the liver to reconvert liberated iron and in *P vivax* infections the selective parasitization of reticulocytes

In chronic malaria there is characteristically a moderate leukopenia with an absolute increase in the number of monocytes

Malarial pigment is taken up by circulating polymorphonuclear leu kocytes and monocytes and is deposited in the reticuloendothelial cells of the viscera One of the striking features of the gross pathologic process in patients who have died after prolonged infection is a slaty or blackish pigmentation of the organs especially the spleen liver and brain (Fig VI 38)

The spleen varies in size color and consistency depending upon the duration and severity of the infection Usually it is enlarged and dark or slate colored After long continued infections it may weigh 1000 grams or more In acute malaria the spleen is congested and soft the capsule is distended and occasionally spontaneous or traumatic rupture may occur In fatal cases there may be hemorrhagic areas of the pulp thrombi in the arterioles and areas of infarction The majority of cases show dis tinct diminution in the size of the splenic follicles In chronic cases fibrosis of the trabeculae is prom nent There is marked hyperplasia of the reticuloendothelial elements

The presence of malarial pigment in these phagocytic cells is a salient microscopic feature Both phagocytosed and free pigment are concen trated in the trabeculae and are also found in the red pulp however it is unusual to find phagocytosed pigment in any part of the follicle From one to 50 or more granules of pigment may be present in the cytoplasm of a single cell The pigment usually appears as single round dark brown blocks (characteristic of *P falciparum*) or as small black conglomerate masses in the phagocyte (Fig VI 38) Hemozoin must be distinguished from iron pigment which may be present in the same cell by the lighter color of the iron and from formalin pigment by the irreg ular crystalline shape of the formalin Dark yellow hemosiderin may be seen in the spleen pulp but not in the malpighian corpuscles

The liver is usually somewhat enlarged and dark in color On micro scopic examination the endothelial and Kupffer cells are seen to be packed with black pigment The cells of the parenchyma may contain considerable amounts of hemosiderin and show cloudy swelling and vacuolization *Malarial pigment is not present in the hepatic parenchymal*

cells Occasionally necrotic foci are seen in the portal areas and in the central zones of the liver lobules (Fig. VI.39)

The brain is frequently lead colored because of the malaria pigment Engorgement of the cerebral capillaries is a prominent feature the capillary network of the brain is distended with erythrocytes There may be extensive capillary plugging by masses of parasitized red cells

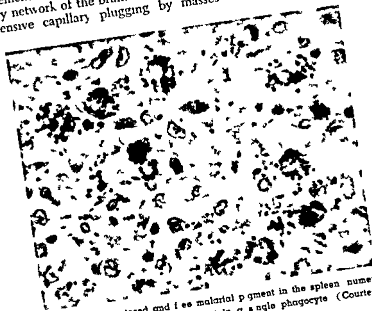


Figure VI.38 Phagocytosed and free malarial pigment in the spleen numerous individual granules and aggregates of pigment in a single phagocyte (Courtesy of the Louisiana State University School of Medicine)

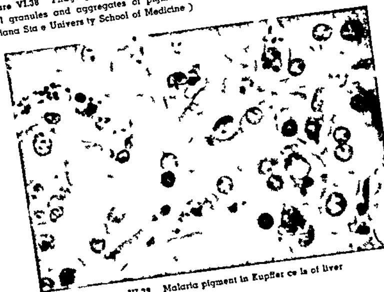


Figure VI.39 Malaria pigment in Kupffer cells of liver

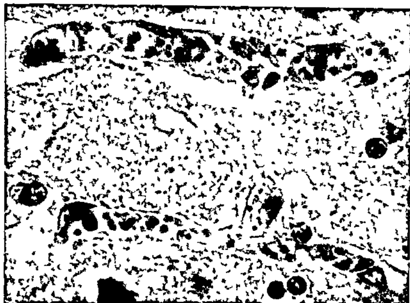


Figure VI 40 Agglutinated parasitized erythrocytes in capillaries of brain—falciparum malaria

(Fig VI 40) In vessels of larger caliber, erythrocytes containing post ring forms of *P falciparum* owing to their adhesive nature, may be seen in contact with the endothelial lining while the noninfected red cells occupy the lumen This arrangement of the parasitized corpuscles is referred to as margination (Fig VI 41 A, B) In fatal cases hemorrhages are found in the subcortical white matter but not in the gray matter They are also seen commonly in the pons medulla and cerebellum These take the form of ring hemorrhages encircling an area of necrosis in which a central plugged vessel may be discerned In addition, malarial granulomas (Durck s nodules) frequently are present These noninflammatory granulomas resemble the areas of simple hemorrhage except that with the initiation of a reparative process a single or multiple layered ring of neuroglial cells is interposed between or mixed with the hemorrhagic belt and the necrotic zone which surrounds the remains of the small central vessel (Fig VI 41 C)

Toxic acute focal or interstitial myocarditis with capillary obstruction in the myocardium may also be present in fatal cases In the presence of prominent gastrointestinal symptoms lesions in the stomach and intestines are not uncommon These are punctate hemorrhages, capillary obstruction by parasitized erythrocytes, necrosis of epithelium and occasionally hemorrhage into the lumen The bone marrow may reveal large numbers of parasitized cells and considerable amounts of malarial pigment

Acute malaria may be associated with profound disturbances of body chemistry There is reduction of the total plasma proteins with reversal of the albumin globulin ratio but usually not above unity The serum

euglobulin is increased Cholesterol lecithin and glucose rise during the chill but are usually slightly decreased during the afebrile period Plasma potassium is greatly increased by the rupture of erythrocytes There is a decrease in levulose and galactose tolerance indicating disturbance of the glycogenetic function of the liver In heavy infections bilirubin may be discharged into the blood plasma in considerable quantities producing an indirect van den Bergh reaction The blood urea ordinarily does not undergo significant change in malaria however when there is sufficient damage to the kidneys in malignant *falciparum* chronic malaria or blackwater fever to interfere with renal function varying degrees of nitrogen retention and uremia may occur

Clinical Characteristics Salient features of malaria are periodic fever splenomegaly anemia and leukopenia The characteristic periodicity of the fever (in *vivax* and quartan infections) is associated with the rhythmic maturation of the sporulating forms in the blood and their massive release by rupture of the erythrocytes The enlargement of the spleen and to a lesser degree of the liver is correlated with an increase in reticuloendothelial cells which as one mechanism of immunity in malaria phagocytose not only merozoites upon their release but also parasitized and nonparasitized red corpuscles Malarial pigment to

normochromic anemia Some patients with acute malaria have herpes labialis others with chronic malaria may have urticaria

The clinical phenomena accompanying infection by *P falciparum* differ greatly in their evolution and in the hazard to the infected individual from those accompanying infection by *P vivax* *P malariae* or *P ovale* *Falciparum* malaria often called malignant tertian is always dangerous and may be fatal The other types although capable of producing severe illness are commonly free from dangerous complications and grave menace to life The term *benign tertian* is therefore often applied to infections by *P vivax* This difference in part at least is due to special characteristics of *P falciparum* Its capacity to invade both mature erythrocytes and reticulocytes is probably directly related to the intense and rapidly

tion Furthermore t

\141)

to 15

days *falciparum* 11 to 14 days *ovale* 14 to 26 days and quartan about four weeks Prodromes consisting of malaise muscle pains headache anorexia and slight fever may exist for a few days before the onset of the acute phenomena In many instances however the initial attack comes on abruptly without prodromes

Vivax and Quartan Malaria The classic clinical picture of malaria with its alternation of "good" and "bad" days is much more the exception

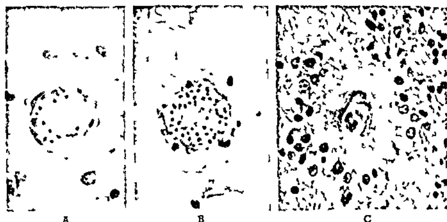


Figure VI.41 A. Vessel of brain with parasitized erythrocytes in contact with the endothelial lining (margination) and noninfected red cells occupying the center of the lumen. A pigment granule of *P falciparum* is prominent in each of the parasitized cells

B Margination with double or multiple rows of adhesive parasitized red corpuscles partially occluding the lumen of the vessel

C Malarial granuloma composed of a central thrombosed vessel necrotic intermediate zone and peripheral rows of neuroglial cells mixed with erythrocytes (Durck's nodule) (Courtesy of the Louisiana State University School of Medicine)

than the rule Even in *P vivax* infections the initial clinical attack seldom exhibits tertian fever at the outset, there are usually two groups of parasites out of phase with one another and these, maturing on alternate days, produce daily, or quotidian, rather than tertian fever Later, one group may drop out and the release of a new generation of parasites will then occur on alternate days, at intervals of 42 to 47 hours Only then does the fever become tertian (Fig VI 42)

The typical paroxysms of benign tertian and quartan malaria are similar except for the difference in periodicity The onset is abrupt and frequently initiated by a rigor which may vary from a slight subjective chilliness to a frank chill accompanied by a sensation of extreme cold although the temperature meanwhile rises rapidly to 104° to 106° F The pulse is rapid and of small volume Polyuria, nausea and vomiting are common After 20 to 60 minutes the hot stage begins, accompanied at first by relief from the sense of intense cold, but shortly followed however, by an increasing and severe headache and a sensation of intense heat At this stage the face is flushed and the pulse full Epigastric discomfort, nausea and vomiting are more prominent There is frequently mild delirium, and although the temperature does not remain long at the fastigium the sweating stage, ushered in by the appearance of moisture on the previously dry skin, increases to a profuse diaphoresis of the entire body With this change the temperature falls rapidly and the pulse returns to normal This is frequently followed by sleep after which the individual awakes somewhat exhausted but otherwise feeling well The sweating stage lasts two to three hours and the entire paroxysm averages ten hours

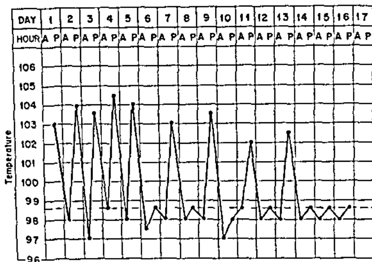


Figure VI.42 Fever chart in a P vivax infection showing an initial quotidian tendency becoming tertian. No specific therapy prescribed (Russell West and Manwell Practical Malariology)

During the paroxysm there is a moderate leukocytosis whereas in the afebrile period leukopenia with an increase in the number of large mononuclears is usual

In quartan malaria the attacks occur every 72 hours The rise of temperature is less abrupt and the total duration of the paroxysm averages 11 hours

Anemia is a common complication of any type of malaria In addition rupture of the spleen may occur in *vivax* malaria but is not common Nephrosis with large amounts of albumin in the urine occurs in chronic malaria chiefly in *P malariae* infections

Falciparum Malaria The onset of malignant tertian malaria is frequently insidious The individual complains of gradually increasing headache of gastrointestinal symptoms or of a clinical complex that is suggestive of influenza and frequently misdiagnosed unless examination of the blood is carried out In other instances onset is abrupt and dramatic Characteristically there are a sensation of chilliness rather than a frank chill a prolonged and intensified hot stage and lack of the marked terminal sweating with its accompanying drop in temperature characteristically observed in *P vivax* infections The fever curve frequently shows prolongation of the fastigium often with primary fall and secondary rise before returning to or toward normal This double peaked elevation is characteristic when it is observed Frequently however the fever is continuous or remittent instead of intermittent During the periods of remission there is little or no return of the sense of well being Commonly the tertian periodicity of the infection is indicated by exacerbation of a continuous fever Defervescence in *falciparum* malaria frequently occurs by lysis rather than by crisis In those instances in

which the fever curve is intermittent the paroxysm often lasts 20 to 36 hours These variations in the fever curve are to be explained by the phenomena of anticipation and retardation of the events of schizogony as a result of which the new generation of parasites is released over a prolonged period

Prostration is more marked and the tendency to delirium greater than in benign tertian and quartan infections Nausea and vomiting frequently occur and the spleen is generally palpable and tender The parasite density in the peripheral blood can vary widely in a few hours and it may be necessary to make repeated smears at intervals of several hours to determine the maximum number of parasites

Pernicious Types *Falciparum* malaria is notorious for its tendency to produce s [illegible]
of disease to [illegible]
applied The [illegible]
adequately treated Several clinical types are known

BILIOUS REMITTENT FEVER The onset is characterized by marked nausea and profuse continuous vomiting Jaundice customarily appears about the second day earlier than in yellow fever and later than in blackwater fever The urine frequently contains bile pigment and yields a yellow foam test Epigastric distress and liver tenderness are marked, and hemorrhage from the stomach may occur producing coffee ground vomitus The temperature tends to be high and the fever curve is usually remittent rather than continuous Dehydration and disturbance of the alkali reserve and of mineral balance may develop rapidly

CEREBRAL MALARIA The onset of cerebral malaria may be sudden or gradual and the clinical picture may be varied The patient may complain of progressively increasing headache with little or no fever and then gradually lapse into coma or a clinical picture in which there appears little cause for immediate concern may be superseded without warning by a progressive and uncontrollable rise of temperature to levels in excess of 108° F In addition to hyperpyrexia convulsive seizures are common Involvement of the cranial nerves may be evident Delirium may occur These clinical phenomena may occur within a few hours and may rapidly become fatal In some instances the onset may be sudden and characterized by mania or other acute psychotic manifestations The initial stages of cerebral malaria have not infrequently been mistaken for acute alcoholism The results of such a diagnostic error are usually disastrous

The extensive interference with the vascular supply to the central nervous system in cerebral malaria with vascular thrombosis and consequent local ischemia and anoxemia may produce any combination of symptoms and signs indicative of severe and extensive involvement of the brain In children convulsions are a frequent presenting symptom There are no constant or significant changes in the spinal fluid The spinal fluid pressure however may be considerably elevated above normal In such instances repeated lumbar drainage is an important therapeutic procedure

ALGID MALARIA The algid forms of *falciparum* malaria accompany extensive vascular involvement of the gastrointestinal tract and other abdominal viscera Profound prostration, with a tendency to fatal syncope, marked coldness of the skin, subnormal temperature and circulatory collapse occur Jaundice may be present Severe grades of anemia may develop rapidly Acute diarrhea unaccompanied by fever and often ending fatally has long been recognized as an algid form of pernicious malaria

Other recognized types of pernicious malaria are the gastric, which is characterized by persistent vomiting, and the dysenteric, in which there is a bloody diarrhea due to extensive capillary thrombosis in the intestinal walls The blood in the stools frequently contains immense numbers of parasites

The general mortality for the pernicious forms of *falciparum* malaria may be as high as 50 per cent

Diagnosis. The diagnosis of malaria is frequently difficult It may be confused with many diseases, both cosmopolitan and tropical This situation is inevitable in view of the pathologic changes, which consist mainly of mechanical interference with the vascular supply in many organs of the body Among the tropical diseases it may be confused with kala azar, amebic liver abscess, relapsing fever and yellow fever Among the cosmopolitan diseases it may frequently simulate typhoid fever, tuberculosis, brucellosis, influenza, pyelitis and other septic conditions including malignant endocarditis as well as acute or chronic organic disease of the central nervous system Malaria is commonly associated with positive Wassermann and Kahn reactions

Definitive diagnosis depends upon demonstration of the parasites For this purpose the thick blood film is far superior to the thin film technique, since in light infections it may be impossible to find plasmodia in the thin film The thick film will yield three to four times as many positive findings and will reveal the plasmodia in virtually all active clinical cases (Diagnostic Methods, pp 797–799) It may be necessary to examine stained thin blood films for positive identification of the particular species present

Other characteristics of the stained thin blood films may be suggestive Leukocytes containing ingested malarial pigment may be seen There is often a leukopenia with a relative increase of monocytes In chronic cases a sustained submaximal reticulocyte crisis beginning four to seven days after the institution of specific therapy is suggestive

Periodicity of the febrile curve and splenomegaly should arouse suspicion of malaria In chronic cases, however, there may be little if any significant splenic enlargement Sternal puncture and examination of the stained marrow smear may be useful in the rare case where parasites cannot be found on a thick blood film

In view of the marked differences in severity and prognosis between *falciparum* malaria and the other forms of the disease, accurate identification of the species of *Plasmodium* is essential The following table presents the significant differential characteristics which may be seen in the stained thin blood film

Because of the importance of the thick film in the differential diagnosis

Table VI 8 Differential Characteristics of the Plasmodia of Man in Stained Thin Films

CHARACTERISTICS	*P falciparum*	*P vivax*	*P ovale*	*P malariae*
Infected erythrocyte enlarged	−	+	±	−
Infected erythrocyte fimbriated and/or oval	Rare	Rare	Frequent	Rare
Infected erythrocyte decolorized	−	+	+	−
Infected erythrocyte Schüffner s dots*	−	+	+	−
Infected erythrocyte Maurer s dots*	+	−	−	−
Multiple infections in erythrocytes*	+	Rare	−	−
Parasite all forms in peripheral blood	Rare	+	+	+
Parasite large coarse rings	−	+	+	+
Parasite double chromatin dots*	+	Rare	−	−
Parasite accolé forms*	+	Rare	−	−
Parasite band forms*	−	−	+	+
Parasite sausage shaped gametocytes	+	−	−	−
Number of merozoites	8 24	12 24	8 12	6 12

* Not invariable but suggest e when seen

of human malaria the characteristics of the three principal species are summarized in Table VI 9 (pp 336–337)

Prognosis. The prognosis for recovery from the primary attack of malaria due to *P vivax*, *P malariae* or *P ovale* is excellent *Falciparum* malaria carries a good prognosis if adequately treated untreated its mortality is sometimes very high Radical cure of malaria in the great majority of cases is possible with proper use of the new antimalarial drugs

Treatment. Drugs have several functions in malaria treatment of clinical attack, curative therapy to prevent relapses suppressive and prophylactic action to prevent the acquiring or the clinical manifestations of the disease and sporontocidal effect which prevents transmission by mosquito vectors There are several drugs exerting some of these effects but no one exerts all The chemical groupings of the drugs are cinchona alkaloids—quinine 4 aminoquinolines—chloroquine, amodiaquine 8 ami noquinolines—primaquine, pamaquine, 9 aminoacridines—mepacrine biguanides—proguai

CHLOROQUINE

crystalline powder

available in tablets for oral administration each 0 25 gram equivalent to 0 15 gram of base, and in ampules of 3 ml containing 50 mgm eq s use

taken by

discolor

the skin Chloroquine is usually well tolerated in the dosages used clinically In certain individuals it may cause mild transient headache visual disturbances pruritus trivial gastrointestinal complaints psychic stimulation and rarely a lichen planus like eruption When given intra venously undiluted there is a fall of systolic blood pressure with little or no change in the diastolic pressure When well diluted and given

slowly no significant change occurs Excretion is accelerated by acidification of the urine

Chloroquine is highly active against the erythrocytic forms of the plasmodia, although *P malariae* responds more slowly than the other species *Falciparum* gametocytes are not removed or sterilized

Chloroquine and amodiaquine are the drugs of choice for treatment of acute malaria In the majority of cases fever is controlled within 24 hours, and thick blood films usually become negative in from 48 to 72 hours Chloroquine will terminate infection by *P falciparum* Since *P vivax* infections have a persisting exo erythrocytic phase, the use of primaquine in conjunction with chloroquine will prevent relapses of *vivax* malaria in the great majority of cases Chloroquine is an excellent antimalarial for suppressive therapy

AMODIAQUINE Synonyms Camoquin, Cam aqi The drug is prepared as the hydrochloride and is distributed in tablets each containing 0 2 gram of amodiaquine base

It is a yellow crystalline powder and has a bitter taste It forms a 5 per cent solution in water at room temperature and is rapidly absorbed from the gastrointestinal tract Amodiaquine is virtually free of toxic effects at normal dosages, although long continued administration in amounts considerably above the recommended therapeutic dosage may be accompanied by loss of energy insomnia, epigastric discomfort and anorexia Its action upon the parasite is similar to that of chloroquine Good results have been reported in the treatment of acute malaria using a single dose of 0 6 to 1 0 gram for adults The recommended dose for children is 10 mgm per kilogram of body weight Amodiaquine has likewise proved to be an efficient suppressive agent For this purpose a single dose of 0 6 gram taken once every two weeks has proved sufficient under most conditions

QUININE This is a general protoplasmic poison It is rapidly absorbed from the gastrointestinal tract 60 to 70 per cent is oxidized in the body and the remainder rapidly excreted in the urine Indications of poisoning appear when the blood level rises to about 10 mgm per 100 ml

Quinine destroys the parasites less rapidly than the 4 aminoquinolines For many years it was the standard drug for treating malaria and it is still used in some countries where the higher costs of the other drugs are a factor or where the quinine industry exists

In therapeutic doses it has little effect on the circulatory system In excessive dosage it produces an initial rise in pulse rate and blood pressure followed by a depression of both When given intravenously in too large a dosage or too quickly, rapid progressive fall of blood pressure occurs with the appearance of circulatory collapse due to cardiac depression and vasodilatation

Cinchonism is the expression of the toxic action of quinine upon the central nervous system It is characterized by mental depression, giddiness, headache, sense of fullness in the head, tinnitus, deafness amblyopia and occasional blindness There may be mental confusion and somnolence as well True idiosyncrasy to quinine results in the symptoms

Table VI.9. Differential Diagnosis of Malarial Parasites in Stained Thick Blood Films*

STAGE OF PARASITE	PLASMODIUM FALCIPARUM	PLASMODIUM VIVAX	PLASMODIUM MALARIAE	COMMENTS
Small trophozoite (early ring)	Small size rings with small chromatin dot and delicate scanty cytoplasm. *Frequently rings have double chromatin dots.* Tendency toward large number of rings. Many ring forms with no older stages—practically certain to be *falciparum* infection. Diagnosis on small number of rings may often be assisted by finding distinguishing gametocyte though this stage is not necessarily present	Larger heavier ring form than in *falciparum*, often with variety of *cytoplasmic pattern and irregularities in shape. Usually older stages parasite* can be found also	Ring is likely to be heavy with large dot of chromatin and small amount *of cytoplasm which is often filled in without a vacuole.* Pigment forms early and may appear as haze in cytoplasm of this stage. Rings practically always associated with older forms. The ring phase is brief so this stage is not found as often as older stages.	Ring forms often not complete circle—may be "swallow" forms, exclamation mark, comma forms or interrupted rings. When rings only are present and number is small it is practically impossible to differentiate species.
Growing trophozoite	Heavy large ring forms—resemble young rings of *vivax*. Sometimes show pigment grains or haze rather clearly in cytoplasm	Stage usually ameboid in appearance with large variety of shapes. Cytoplasm frequently fragmented and arranged irregularly in cluster of varying sized pieces or streamers, about or close to a large chromatin mass. Small yellowish brown pigment granules scattered through parts of the cytoplasm. This is the most characteristic stage of *vivax*. Frequently other younger or older stages accompany this one.	Small, usually rounded compact forms like marbles in a ring. Profuse heavy dark large-grained pigment. Forms frequently so solid that chromatin seems buried in the mass. This stage and the one that follows are the commonest forms of this parasite seen	In heavily stained films and in films which have been kept for several days before staining the "ghost" of the enlarged host cell and persistence of Schüffner's stippling or a pinkness remaining from the stippling may assist in diagnosis of *vivax*
Large trophozoite	Ring vacuole lost or almost lost. Parasite quite small and compact cytoplasm often quite pale, irregularly circular or oval. One large chromatin dot. Pigment in blurred mass or small very dark clump or clumps. Stage is usually found only when the infection is intense and usually accompanied by numbers *of ring form trophozoites.*	Frequently quite solid and dark staining. More or less irregular in outline possibly with one or more vacuoles. Fine brown pigment scattered throughout the cytoplasm. May be confused with macrogametocyte	Compact dark larger than growing stages. Sometimes in thinner portion of the smear spreads to normal size. Profuse fairly coarse dark brown pigment—often masking the chromatin. May be confused with rounded up *falciparum* gametocyte or with gametocyte of *malariae*	On rare occasions Maurer's dots have been observed in thick films of *falciparum*. The infrequently found stages of *falciparum* are of course more readily found in thick films. Band forms have tendency to become rounded in thick films of *malariae*—except perhaps in very thin edge of smear
Schizont (presegmenting)	Stage not often seen and is usually accompanied by large numbers of growing trophozoites when present. Parasite is very small. Contains 2 or more divisions of chromatin and very little cytoplasm (often pale) in which there is located one or more small dense blocks of very dark pigment	Irregular or compact clusters of chromatin divisions often dark reddish-purple in color. Cytoplasm in irregular broken masses and wisps containing light brown pigment granules which are clumping in spots. Usually accompanied by other stages. May be confused with same stage of *malariae*	Much like *vivax* of the same stage *except that parasites are often* smaller with darker larger pigment granules. Often so compact that internal structure is difficult to define. Usually accompanied by other stages. May be confused with presegmenting schizonts of *vivax*	Schizonts are much like thin film *forms of same stages*—more compact, smaller in thicker portions of smear. This is most difficult stage (except infrequent ring forms) on which to diagnose species.

Mature schizont	Seldom seen except in severe cases. Always associated with many small trophozoites. Usually contains around 20 or more tiny merozoites clustered around a small, very dark, pigment mass	Usually contains around 16 merozoites which are individually larger than those of *falciparum* Usually relatively larger than other species. Nearly always associated with other stages Not so often found as other stages	Most distinctive stage of *malariae* in thick film. Often found in large numbers—usually with trophozoites or presegmenting forms or both. About 8 merozoites each with large chromatin dot and small amount of cytoplasm—may be compact or clearly separated. Frequently the chromatin and pigment only are seen, the chromatin dots being bare and well separated. The dark heavy pigment is more often concentrated, though sometimes dispersed	*Usually smaller* than same stage in thin film.
Young gametocyte	Sometimes long, slender and pointed, with pigment scattered to the ends. Usually associated with many trophozoites.	When found is a small, compact, usually rounded parasite, with one chromatin mass which is often in the center of cytoplasm and frequently has unstained area around chromatin mass. Sex is almost impossible to determine	Same as *vivax* except that parasite is even less frequently found and resembles compact trophozoite so closely that differentiation is absolutely impossible	
Mature gametocyte	Differentiation of sex is difficult or impossible. As 'crescent' or "sausage" shapes, may be quite diagnostic of species. In thicker portion of smear may take on oval or rounded, somewhat eroded appearance, which may be confused with *malariae* trophozoite or gametocyte. Often may be distinguished by difference in amount and appearance of pigment or by pink or red "flag" protruding from the edge of the parasite. May be accompanied by ring form trophozoites or appear alone and infrequently. Often appears in 'showers'	Macrogametocyte is *larger, as a rule,* than in other species. Pigment is light, delicate, well dispersed through nonvacuolated cytoplasm. Except in thin edge of film cannot be differentiated from some mature trophozoites of same species. Microgametocyte often distinguishable as large blob of chromatin (varying from pink to purplish red) surrounded by halo of pale or colorless cytoplasm in which pigment granules are more or less evenly dispersed. Other stages of the parasite can usually be found	*As a rule, few in number, somewhat* smaller than *vivax*, otherwise have the same distinguishing features except that pigment is coarser and darker. May resemble rounded *falciparum* gametocytes.	

* Courtesy of Aimee Wilcox, Laboratory of Tropical Diseases, Microbiological Institute, National Institutes of Health in "Manual for The Microscopical Diagnosis of Malaria in Man" 2nd ed., 1950, and the American Public Health Association, Standard Methods Committee on Diagnostic Procedures and Reagents 'Diagnostic Procedures and Reagents.' 2nd ed., New York, 1945

of cinchonism after small doses which are well within the normal ther apeutic range

PRIMAQUINE DIPHOSPHATE This drug is chemically related to pama quine but is less toxic It is an orange crystalline solid with a bitter taste and is slightly soluble in water It is supplied in tablets 26 5 mgm of the salt being equivalent to 15 mgm of the base

Like pamaquine the drug has a dangerous toxic potential In over dosage or in susceptible individuals it produces severe hemolytic reac tions The Negro race is particularly susceptible Anemia methemo globinemia and leukopenia should be watched for during therapy by repeated blood and urine examinations Primaquine should be discon tinued immediately if signs suggestive of hemolytic anemia occur such as darkening of the urine or a significant fall of hemoglobin or of the erythrocyte count Quinacrine appears to increase the toxicity The two drugs should never be used together and primaquine should not be given to a patient who has received quinacrine until the latter drug has been excreted

Primaquine is active against the exo erythrocytic stage of *P vivax* It is relatively ineffective against the erythrocytic forms of the plasmodia Its use is restricted to the prevention of relapses

PAMAQUINE Synonyms Plasmochin Plasmoquine Pamaquine is rapidly absorbed when taken by mouth and is excreted in the urine It regularly causes some degree of methemoglobinemia and may precipitate serious hemolytic crises especially if given in conjunction with quinacrine or primaquine It is more toxic for Negroes than Caucasians

It has been used in the past to sterilize the gametocytes of *P falci parum* and to limit the relapses of *vivax* malaria It has been displaced by the newer antimalarial drugs It is not recommended especially in view of the narrow margin of safety between the therapeutic and toxic dosage

PROGUANIL Synonyms Chlorguanide Guanatol Paludrine Pro guanil hydrochloride is a colorless bitter pyrimidine compound which is rapidly absorbed from the gastrointestinal tract and is excreted in the feces and urine There are no significant toxic effects at therapeutic dosage levels

Chlorguanide is a slowly acting schizonticide which inhibits chromatin division It inhibits the development of female gametocytes in the mos *quito thus interrupting the exogenous cycle of the plasmodia Resistant* strains of plasmodia have been produced in the laboratory and in the field It is an effective therapeutic agent against nonresistant strains but slower in action than chloroquine quinine or quinacrine The effective ness however varies between different geographic areas In general the fever is controlled and trophozoites disappear from the peripheral blood in the course of 48 to 72 hours In many instances but not in all a single course of therapy terminates infection by *P falciparum*

It is not the drug of choice for the treatment of acute clinical malaria especially since the serious complications are brought under control only slowly

PYRIMETHAMINE Synonyms Daraprim Malocide Pyrimethamine is chemically related to chlorguanide It is a tasteless odorless freely soluble white powder The drug is concentrated in the liver spleen brain and bone marrow It is entirely free from toxic or unpleasant side effects at recommended dosage levels When administered in amounts far exceeding therapeutic levels it produces megaloblastic changes in the marrow inhibition of leukopoiesis reduction of erythrocyte and leukocyte counts atrophy of lymphatic tissue and degenerative changes in the intestinal epithelium

than that of chloroquine or amodiaquine Furthermore in certain areas it has not proved effective against the local strains of *P falciparum*

MEPACRINE HYDROCHLORIDE Synonyms Atabrine quinacrine Mepacrine is a yellow acridine dye with a bitter taste It is soluble in water The dihydrochloride Atabrine is absorbed rapidly deposited in the tissues especially the liver and gallbladder and causes a yellow discoloration of the skin Excretion is slow The drug is present in the breast milk of nursing mothers

Mepacrine (quinacrine) is usually well tolerated although in certain individuals it acts as a gastrointestinal irritant causing epigastric pain nausea vomiting and diarrhea These symptoms are usually transient phenomena that may be controlled by giving the drug with food or sweetened fluids With rare exceptions mepacrine may be taken over long periods without ill effect Rarely dermatitis occurs This may take the form of atypical lichen planus eczematoid or exfoliative lesions There may be leukoplakia or pigmentation of the mucous membrane of the mouth Mepacrine should not be administered in conjunction with pamaquine or primaquine because of the danger of acute hemolytic crises

The drug is active against the erythrocytic forms of the plasmodia Although a single course of therapy will commonly terminate infections by *P falciparum* it is not as effective as the 4 aminoquinolines It does not affect the relapse rate of *vivax* or *malariae* malaria and when taken as a suppressive will prevent *falciparum* malaria

It is an efficient suppressive agent when taken in dosage of 0 1 gram daily Clinical attacks begin to appear about two weeks after discontinuing the medication

Treatment of Clinical Malaria *Falciparum* malaria in the nonimmune individual is a highly dangerous infection which requires immediate and effective therapy The grave complications presented by the pernicious forms of the disease may develop with great rapidity and are commonly accompanied by high mortality rates Acute *falciparum* malaria and the paroxysms of *vivax* malaria are frequently accompanied by profuse nausea and vomiting Particularly in the former it may be necessary to initiate treatment by parenteral therapy This however should

Table VI.10. Treatment of Clinical Malaria

TREATMENT SCHEDULES

The doses suggested in this summary are for adults of approximately 150 lb (70 kg) bodyweight In general they should be adjusted according to the usual rules for weight and age The doses recommended for prophylaxis and suppression in children are reduced according to age

TREATMENT OF CLINICAL ATTACK IN NONIMMUNE SUBJECTS

1 *Chloroquine diphosphate* or *sulfate* 600 mgm of base 300 mgm six hours later 300 mgm daily for next two days

OR

2 *Amodiaquine dihydrochloride dihydrate* 600 mgm of base first day, 400 mgm daily for next two days

OR

3 *Mepacrine dihydrochloride dihydrate* 1 gram (five doses of 200 mgm) first day 100 mgm thrice daily for next six days

OR

4 *Quinine sulfate* or *dihydrochloride* 1 3 to 2 grams (20 to 30 grains) daily for five to seven days

EMERGENCY TREATMENT

1 *Chloroquine hydrochloride* 200 to 300 mgm of base intramuscularly repeated in [illegible]

repeated in eight hours if necessary *An effective blood level is however, rapidly attained by the intramuscular route* which is generally to be preferred Transfer to oral therapy as soon as possible

OR

2 *Quinine dihydrochloride* 650 mgm (10 grains) in normal saline glucose saline or plasma injected intravenuosly *very slowly* (not more than 50 mgm of salt per minute) repeated in six hours if necessary not more than three injections in 24 hours *Or* the drug may be administered by intravenous drip at the rate of 2 grams (30 grains) in 24 hours Transfer to oral therapy as soon as possible

OR

3 *Mepacrine methane sulfonate* given intramuscularly in single doses not exceeding 300 mgm total in first 24 hours 600 to 900 mgm Transfer to oral therapy as soon as possible

TREATMENT OF CLINICAL ATTACK IN SEMI IMMUNE SUBJECTS

1 *Chloroquine diphosphate* or *sulfate* 600 mgm of base single dose

OR

2 *Amodiaquine dihydrochloride dihydrate* 600 mgm of base single dose

OR

3 *Mepacrine dihydrochloride dihydrate* 400 mgm 200 mgm four hours later 300 mgm daily for next three days

4 *Quinine sulfate* or *dihydrochloride* 1 0 to 1 5 grams (15 to 23 grains) daily for two to five days

Table VI.10. Treatment of Clinical Malaria (Cont d)

RADICAL CURE OF VIVAX AND MALARIAE INFECTION

1 *Primaquine diphosphate* 15 mgm of base daily, in single or divided doses, for 14 days, reinforced by standard treatment with a schizontocidal drug* if given during an acute attack (do not give to children under six years of age)

OR

2 *Pamaquine naphthoate* or *monohydrochloride* 8 to 10 mgm of base thrice daily for ten to 14 days reinforced by standard treatment with a schizontocidal drug* if given during an acute attack

PROPHYLAXIS AND SUPPRESSION**

1 *Chloroquine diphosphate* or *sulfate* 300 mgm of base once weekly

OR

2 *Amodiaquine dihydrochloride dihydrate* 400 mgm of base once weekly, for partially immunes, 400 to 600 mgm every two weeks

OR

3 *Proguanil monohydrochloride*† 100 mgm daily‡, *or* for partially immune subjects, 300 mgm once weekly

OR

4 *Pyrimethamine*† 25 mgm once weekly, do not give to children under one year of age

OR

5 *Mepacrine dihydrochloride dihydrate* 100 mgm daily, *or*, for partially immune subjects 300 mgm once weekly Administration *beginning ten days before exposure to infection*

OR

6 *Quinine sulfate* or *dihydrochloride* 650 mgm (10 grains) daily *Recommended only when none of the above listed drugs is available*

* Mepacrine should not be given *concurrently* with any of the 8 aminoquinoline drugs

** The prophylactic regimen should be continued for one week after leaving an endemic area where proguanil or pyrimethamine has been used and for one month is the case of other drugs

† The use of proguanil or pyrimethamine is contraindicated in areas where resistance to *either* of these drugs is known to exist

‡ In parts of Africa this dosage has been found insufficient in Nigeria for instance the following scale has been recommended adults, 100 to 200 mgm daily, children 0–1 year 50 mgm three to six times weekly, 1–3 years, 50 mgm daily, over 3 years 100 mgm daily

be superseded as early as is practicable by oral medication The drug regimens are shown in Table VI 10

PREVENTION OF RELAPSES OF VIVAX MALARIA Relapses of *vivax*

cation for discontinuing medication Particular caution is required in the case of Negro patients (Table VI 10)

Suppressive Treatment. Although prevention of infection is not possible clinical attacks of *vivax* and *malariae* malaria can be held in

Table VI.10. Treatment of Clinical Malaria

TREATMENT SCHEDULES

Th

boc

anc

duc

TREATMENT OF CLINICAL ATTACK IN NONIMMUNE SUBJECTS

1 *Chloroquine diphosphate* or *sulfate* 600 mgm of base, 300 mgm six hours later, 300 mgm daily for next two days

OR

2 *Amodiaquine dihydrochloride dihydrate* 600 mgm of base first day, 400 mgm daily for next two days

OR

3 *Mepacrine dihydrochloride dihydrate* 1 gram (five doses of 200 mgm) first day, 100 mgm thrice daily for next six days

OR

4 *Quinine sulfate or dihydrochloride* 1 3 to 2 grams (20 to 30 grains) daily for five to seven days

EMERGENCY TREATMENT

1 C

six hou

intrav

mgm

repeat

tained

therapy as soon as possible

OR

2 *Quinine dihydrochloride* 650 mgm (10 grains) in normal saline, glucose saline or plasma injected intravenuosly *very slowly* (not more than 50 mgm of salt per minute) repeated in six hours if necessary not more than three injections in 24 hours *Or* the drug may be administered by intravenous drip at the rate of 2 grams (30 grains) in 24 hours Transfer to oral therapy as soon as possible

OR

3 *Mepacrine methane sulfonate* given intramuscularly in single doses not exceeding 300 mgm , total in first 24 hours 600 to 900 mgm Transfer to oral therapy as soon as possible

TREATMENT OF CLINICAL ATTACK IN SEMI IMMUNE SUBJECTS

1 *Chloroquine diphosphate* or *sulfate* 600 mgm of base, single dose

OR

2 *Amodiaquine dihydrochloride dihydrate* 600 mgm of base, single dose

OR

3 *Mepacrine dihydrochloride dihydrate* 400 mgm 200 mgm four hours later 300 mgm daily for next three days

4 *Quinine sulfate or dihydrochloride* 1 0 to 1 5 grams (15 to 23 grains) daily for two to five days

Table VI.10. Treatment of Clinical Malaria (Cont'd)

RADICAL CURE OF VIVAX AND MALARIAE INFECTION

1 *Primaquine diphosphate* 15 mgm of base daily, in single or divided doses, for 14 days, reinforced by standard treatment with a schizontocidal drug* if given during an acute attack (do not give to children under six years of age)

OR

2 *Pamaquine naphthoate* or *monohydrochloride* 8 to 10 mgm of base thrice daily for ten to 14 days reinforced by standard treatment with a schizontocidal drug* if given during an acute attack

PROPHYLAXIS AND SUPPRESSION**

1 *Chloroquine diphosphate* or *sulfate* 300 mgm of base once weekly

OR

2 *Amodiaquine dihydrochloride dihydrate* 400 mgm of base once weekly, for partially immunes, 400 to 600 mgm every two weeks

OR

3 *Proguanil monohydrochloride*† 100 mgm daily†, or for partially immune subjects, 300 mgm once weekly

OR

4 *Pyrimethamine*† 25 mgm once weekly, do not give to children under one year of age

OR

5 *Mepacrine dihydrochloride dihydrate* 100 mgm daily, *or*, for partially immune subjects 300 mgm once weekly Administration *beginning ten days before exposure to infection*

OR

6 *Quinine sulfate* or *dihydrochloride* 650 mgm (10 grains) daily *Recommended only when none of the above listed drugs is available*

* Mepacrine should not be given *concurrently* with any of the 8 aminoquinoline drugs

** The prophylactic regimen should be continued for one week after leaving an endemic area where proguanil or pyrimethamine has been used and for one month is

100 mgm daily

be superseded as early as is practicable by oral medication The drug regimens are shown in Table VI 10

PREVENTION OF RELAPSES OF VIVAX MALARIA Relapses of *vivax* malaria may be prevented in the great majority of cases by the standard course of treatment of the acute attack using chloroquine and concurrent administration of primaquine diphosphate 26 5 mgm, (15 mgm base)

Suppressive Treatment Although prevention of infection is not possible, clinical attacks of *vivax* and *malariae* malaria can be held in

abeyance for prolonged periods by the administration of various anti malarial drugs However following cessation of medication clinical at tacks due to infection by *P vivax* and *P malariae* begin to occur after ten days or two weeks In the case of infections of *P falciparum* sup pressive regimens with certain of the available drugs will eradicate the infection without the development of clinical malaria The routines for suppressive treatment are shown in Table VI 10

To be effective suppressive treatment must be taken regularly A break through of clinical activity will occur when drug administration is irregular or insufficient It may likewise occur in the presence of excessive fatigue acute infections trauma and hemorrhage or exposure to high al titudes since these conditions tend to activate latent malaria Resistance may appear when pyrimethamine and proguanil are used

Blackwater Fever

Blackwater fever is one of the most dangerous complications of ma laria It is characterized by prostrating chills profuse vomiting early jaundice the passage of dark red to black urine and a rapidly developing anemia It is essentially an acute intravascular hemolysis with hemo

curs
odia

may be found in the peripheral blood and the history generally reveals a succession of malarial attacks *Plasmodium falciparum* usually is the species involved

The pathogenesis of the hemolysis in blackwater fever is obscure *Drugs especially quinine have been suggested as important factors* as have immune reactions and sensitization to the malaria parasite

Pathology Sudden destruction of red blood cells occurs and large amounts of hemoglobin are released Although the osmotic fragility of the erythrocytes is not altered there is abnormal fragility to lysolecithin and the red blood cells have a reduced survival time when transfused into a normal individual Erythrocytes from a normal donor when trans fused into a patient with acute blackwater fever are lysed as rapidly as the patient s own cells

The mechanism *for the disposal of blood pigment is overloaded* Hemo globin methemalbumin and hemobilirubin accumulate in the plasma When the renal threshold is reached hemoglobinuria appears and methemoglobin and bile pigments are present in the urine

Renal insufficiency anuria and azotemia have been incorrectly attrib uted to precipitation of hemoglobin and its products in an acid medium causing obstruction of renal tubules Renal anoxia and ischemia are probably of great importance in reducing glomerular *filtration and tubu lar* reabsorption Dehydration increases the hazard of renal failure

The pathologic changes in the viscera are predominantly those of chronic malaria In addition, the liver may show either cloudy swelling or necrosis of parenchymal cells, particularly in the regions of the central veins It is yellowish brown due to hemosiderin

The kidneys are large and black Renal tubules are blocked with debris and hemoglobin casts Cloudy swelling and degeneration of the tubular

ported in patients with clinical evidence of azotemia Granular eosinophilic material may be observed within the collecting tubules (Fig VI 43) Coarse pigmented casts frequently are present in the distal convoluted tubules

Symptomatology. Blackwater fever presents three cardinal symptoms—hemoglobinuria, fever and jaundice The onset is usually sudden, with very severe chill marked prostration, pain over the region of the kidneys and a rapid rise of temperature to 104° or 105° F The fever may be continuous or remittent and rather profuse sweating is apt to accompany drops of temperature Severe nausea and vomiting accompanied by epigastric distress usually appear early and may be continuous and serious Jaundice appears within a few hours after the onset and may become intense if the hemolysis is extensive or long continued Not infrequently the onset of symptoms is accompanied by the desire to void and the urine specimen presents the color characteristic of the disease The pulse is usually rapid feeble and of low tension Pallor proportionate

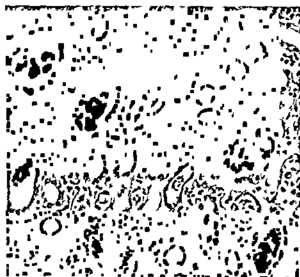


Figure VI 43 Kidney in blackwater fever showing hemoglobin casts in distal convoluted tubules and degeneration and regeneration of tubular epithelium.

to the degree of anemia rapidly becomes apparent, and the red blood count may fall by as much as two million within a period of 24 hours

The clinical course may terminate after one such abbreviated episode, there may be recurring hemolytic crises, or the process may be continuous, extending over several days in the course of which the fever, hemolysis and hemoglobinuria continue

Prognosis. The general mortality rate is 25 to 50 per cent In approximately half the fatal cases death results from renal failure Marked and persistent vomiting and hiccough are unfavorable signs, as are a rising curve of the blood urea and a falling urinary output One attack of blackwater fever seems to predispose to subsequent attacks

Diagnosis. The occurrence of hemoglobinuria, fever and jaundice in an individual known to have had malaria is strong presumptive evidence of blackwater fever Other causes of hemoglobinuria however, must be considered Hemolysis due to pamaquine may be identified by

demonstrate plasmodia, therefore, is insufficient evidence to exclude this condition

In addition to the characteristic color of the urine, microscopic examination reveals the presence of much amorphous sediment, occasional red blood cells and casts of various types Albumin is present in considerable amounts

Treatment. Absolute rest is essential A cardinal rule should be never to move the patient after the onset of the disease A lower mortality rate will be obtained by the institution of limited therapy than by transportation of the patient to a hospital where all necessary facilities may be available

Fluids Dehydration increases the hazard of the disease and must be watched for especially in the presence of severe vomiting Administration of excessive amounts of fluid in the presence of oliguria or anuria may precipitate pulmonary edema It is desirable to maintain a daily urine output of 1200 to 1500 ml, *which may require a fluid intake of 2000 to* 5000 ml Parenteral administration is frequently necessary because of

ours, by

cells rather than plasma have been lost, is the

washed, packed erythrocytes resuspended in normal saline solution

Antimalarial Therapy When malaria parasites are present in the peripheral blood immediate intensive treatment with a rapidly acting plasmocidal drug is essential The drugs of choice are chloroquine and amodiaquine

Quinine mepacrine and 8 aminoquinolines are contraindicated

Administration of alkali in the presence of acid urine has been advocated in the past This practice was based upon the erroneous concept, referred to previously that the oliguria and anuria were the result of the precipitation of acid hematin in the renal tubules producing obstruction It is now recognized that the mechanism of renal insufficiency is quite different and that administration of alkalis is of no value and may be dangerous Diuretics do not increase the urine output in blackwater fever and should not be used

Prophylaxis In the prevention of blackwater fever malaria prophylaxis and adequate treatment of clinical malaria especially when due to *P falciparum* are essential Recognition of the so called *preblack water state* is important This is characterized by toxemia slight jaundice enlargement and tenderness of the liver and abnormally dark colored urine In the presence of this condition hospitalization and careful antimalarial therapy are essential The prevention and control of malaria are discussed on pp 762–765

36

Toxoplasmosis

Synonyms None

Definition Toxoplasmosis is a disease of man and animals produced by the organism *Toxoplasma gondii* (Nicolle and Manceaux) The infection is usually inapparent and unrecognized in adults In children it may take the form of various syndromes in which involvement of the central nervous system or viscera predominates

Distribution Infection is widespread in a variety of animals throughout the world Human infections have been reported from every continent including Europe the Middle East Ceylon North Central and South America Australia and Hawaii

Etiology Toxoplasmosis of man is caused by *Toxoplasma gondii* which was originally described from a North African rodent the gondi All strains recovered from man and animals that have been tested are morphologically and immunologically identical The organism is an obligate intracellular parasite presenting typical morphology and staining characteristics in exudate or impression films of fresh tissue It is patho



Figure VI 44 Toxoplasmata as seen (a) free in stained films of peritoneal exudate or tissue (b) intracellularly and (c) as pseudocyst in film of brain. Wright's stain (800 ×) reduced from a photomicrograph with a magnification of 1 000 diameters (Courtesy of Dr A B Sabin in J A M A vol 116)

genic for small laboratory animals and shows immunologic relationship *with established strains* Parasites fulfilling these criteria have been found in man dogs cats guinea pigs pigeons chickens swine sheep cattle and other avian and mammalian hosts

Toxoplasma gondii may be found free in the body fluids of its host or it may occur as an intracellular parasite of the mononuclear leukocytes endothelial parenchymal and other tissue cells In the free stage *T gondii is typically curved or crescent shaped and measures* 4 to 6 μ in length and 2 to 3 μ in breadth in fresh exudate or on films One extremity is more rounded than the other In fresh preparations it appears as a hyaline body and when recovered from the peritoneal exudate of experimentally infected animals it is found singly or in pairs When stained by Wright's or Giemsa's method the cytoplasm stains blue and the nucleus stands out as a red to *purple irregular mass occupying only one* fifth to one fourth of the cell Typically the nucleus is eccentric and is situated nearer the round end of the parasite (Fig VI 44a)

In the intracellular stages *T gondii* may appear singly or in clusters within the parenchymal and reticuloendothelial cells of many organs When so situated the parasites appear to lose their crescent shape (Fig VI 44b) and may be readily confused with the leishmanias especially *when found in endothelial and mononuclear cells Two principal forms* of intracellular *Toxoplasma can be distinguished They are the prolifera tive forms* and the pseudocysts

Proliferative forms are characteristic of acute and subacute infections They may be distributed throughout the body The parasites multiply intracellularly and are frequently set free by disintegration of the host cell The organisms are loosely grouped with about ten to 30 per cell The maximum number of parasites in a host cell is about 60 The size of the cluster of parasites within the host cell is from 10 to 20 μ There is no argyrophilic limiting membrane about the *host cell*

Pseudocysts are characteristic of chronic or healed infection *This form* is usually found in the brain eye heart muscle skeletal muscle and oc casionally in the adrenal *The toxoplasmata within the pseudocyst are* set free only occasionally The organisms are usually closely packed and there are hundreds of them Pseudocysts are round or spindle shaped

and usually measure from 30 to 50 μ with a maximum of 100 μ There is an argyrophilic wall about the pseudocyst (Fig VI 44c)

Epidemiology Toxoplasmosis may be congenital or acquired In mice the disease has been transmitted experimentally in utero as well as through the milk of lactating females Congenital toxoplasmosis in humans is acquired in utero by transplacental transmission The maternal infection usually is asymptomatic or unrecognized and represents a first or primary infection acquired during that particular pregnancy Toxoplasmic infection of the fetus in subsequent pregnancies is extremely unlikely

Although the actual method of transmission of acquired toxoplasmosis to man is unknown *Toxoplasma* organisms have been transmitted in experimental animals orally and by inoculation (intracutaneous and subcutaneous intravenous intraperitoneal intracerebral and intranasal) This suggests the possibility of transmission by the droplet method or by contact with excreta or infected tissues In the main attempts to incriminate arthropods have been unsuccessful Infections are transmitted between swine and rodents when either animal is fed infected tissue from the other or when pigs ingest infected swine offal From the present evidence it seems probable that infection may be acquired from the con

disease in lower animals Susceptibility in the human is apparently universal

Large scale dye and skin test surveys have been conducted in various parts of the world The results suggest that inapparent infection with *Toxoplasma* is widespread since the percentage of individuals with positive tests increases with age until in some areas after the age of 20 50 per cent or more are positive It has also been demonstrated that the antibody titers may decrease even though the live parasites may be isolated

Pathology The pathology of congenital toxoplasmosis differs from that of the usual infections in adults In the former the acute involve

most commonly in the cerebral cortex and basal ganglia and at times in the periventricular tissue and the spinal cord Depressed yellow areas of necrosis on the surface of the cerebral cortex with the adherent overlying meninges are characteristic Hydrocephalus is a frequent finding Histologically the lesions in the brain are of a chronic granulomatous non suppurative nature with necrosis and calcification

In the usual postnatally acquired infections of adults which are typically inapparent lesions are detected only accidentally In the rare acute cases however they may be widespread throughout the body

Toxoplasma also may cause inflammatory chorioretinal lesions in adults Proliferative forms may multiply in the retina and produce pro

gressive ocular lesions which necessitate enucleation of eyes after they become phthisic *Toxoplasma* usually persists as pseudocysts throughout chronic ocular infection Although apparently inert when intact rupture of the pseudocysts gives rise to intense inflammatory reactions suggesting hypersensitivity

Clinical Characteristics The most commonly recognized clinical picture of human toxoplasmosis is the result of congenital infection in infants and young children It usually appears as a form of encephalitis accompanied by s [illegible]
cephaly microphth [illegible]
tion Convulsions [illegible]
may occur The combination of cerebral calcification and chorioretinitis make the diagnosis of toxoplasmosis most probable

Immunologic studies of human sera indicate that inapparent or unrecognized infections are not uncommon among the adult population Acute clinical toxoplasmosis among adults however is rare but frequently fatal It is usually accompanied by prolonged remittent fever often with such features as pneumonitis suggestive of primary atypical pneumonia encephalitis and myocarditis There may be disseminated myositis accompanied by generalized aching and pain and there may be generalized lymphadenopathy with firm discrete painless lymph nodes Often there is a maculopapular erythematous rash which typically does not appear on the hands feet or scalp

A mild form of the disease resembling infectious mononucleosis characterized by fever lymphadenopathy and monocytosis has been described

Ocular toxoplasmosis may be congenital or acquired Congenital cases may have one or more of the following manifestations acute chorioretinal inflammation at birth or developing soon afterwards esodeviation or exodeviation of the eyes noted early in life amblyopia often recognized for the first time at school examination and late relapse of chorioretinitis occurring during childhood or adult life Acquired ocular toxoplasmosis in adults is characterized by retinochoroiditis which is usually unilateral The fundus inflammation cannot be distinguished from that seen in other diseases Toxoplasmosis accounts for a significant proportion of cases of retinochoroiditis in adults The patients rarely have associated acute systemic infections

Diagnosis *Toxoplasma gondii* may be demonstrated by a variety of laboratory procedures (see p 833) in blood bone marrow cerebrospinal fluid biopsy examination of muscle and lymph nodes or exudates from the serous cavities of patients Usually Toxoplasma can be recovered from suspect patients following intracerebral and intraperitoneal inoculation of laboratory mice Other diagnostic aids include the methylene blue dye technique the complement fixation test and the fluorescent stain for Toxoplasma (pp 834–835) The organisms can also be recovered at necropsy A presumptive diagnosis is generally made by serologic means and confirmed by the inoculation of exudate or blood into laboratory mice The organisms also may be isolated by inoculation of chick embryos and tissue cultures The toxoplasmin intradermal test has limited clinical diagnostic value owing to the high percentage of skin test positives in many areas

Treatment. Combined therapy with pyrimethamine (Daraprim)

then 25 mgm daily was also given Therapy was continued for 14 days Prolonged use of pyrimethamine and sulfonamides is not without danger Biweekly urinalysis for sulfonamide crystals and blood counts for anemia and agranulocytosis should be made Folinic acid may be given to prevent the production of anemia by prolonged use of Daraprim In treatment for ocular toxoplasmosis, the above therapeutics can be accompanied by anti inflammatory corticoid therapy, if lesions are severe enough that scarring may result in visual impairment

37

Interstitial Plasma Cell Pneumonia

Synonyms Parasitic or pneumocystic pneumonia

Definition. This is an unusual type of infantile pneumonia Its etiology is uncertain however, *Pneumocystis carinii* has often been demonstrated in this disease and may be the causative agent

Distribution Human infection has been recognized most frequently in central Europe Cases have been observed also in Canada the United States and South America

Etiology and Epidemiology The taxonomic position of *P carinii* Delanoe and Delanoe 1912 has not been determined It is believed to be a protozoan (Sporozoa Haplosporidia) The most characteristic

aggregate of parasites is pinkish violet the cytoplasm of the individual parasites is violet and the nucleus is dark violet The shape of the individual parasites is either oval or elongate, the nucleus is usually elongate also and often situated marginally The mode of transmission is unknown

In addition to man, *Pneumocystis* occurs in guinea pigs, rats mice, rabbits dogs cats goats and sheep

Pathology. Both lungs usually are involved They are typically pale gray, firm and contain little air Microscopic sections may show

little resemblance to lung tissue since the alveolar septa are so widened by cellular infiltration that many of them press against each other thus presenting a fairly solid and markedly cellular appearance Alveolar spaces may be obliterated completely The alveolar ducts likewise are compressed or filled with exudate Pathologically this disease is characterized by a diffuse interstitial pulmonary infiltration by mononuclear cells which for the most part resemble plasma cells An alveolar exudate is present and contains a foamy or honeycombed material in which *P carinii* may be found The parasites are extracellular

Clinical Characteristics This disease is remarkable clinically in presenting almost no symptoms until late in its course in showing marked predilection for premature or immature infants and for being confined usually to infants from six weeks to four months old The onset is insidious Clinical diagnosis is based chiefly on a gradual onset with increasing tachypnea dyspnea and cyanosis Fever and cough are absent unless aspiration pneumonia develops The respiratory rate in advanced cases is from 90 to 120 per minute Physical examination may reveal areas of fine crepitant rales X ray examination reveals a picture of consolidation atelectasis and emphysema The total leukocyte count and the erythrocyte sedimentation rate are variable The duration of the clinical manifestations is two to three weeks Frequently the mild initial stage is overlooked and the illness is not apparent until a few days before death The mortality ranges from 15 to 60 per cent with death most often due to asphyxia

Diagnosis Routine chest films and respiratory rate counts are the measures of greatest value for early detection of infection in exposed patients in hospital wards when the infection is present At autopsy the best method of diagnosis is by Giemsa stained smears of the alveolar exudate of lung tissue and demonstration of *P carinii*

Treatment Only supportive measures especially oxygen with rest and constant nursing care are of benefit The infection has not responded to antibiotics antimalarials or other protozoacidal drugs

38

The Trypanosomidae

Introduction
only members o
man or animals
flagellates Three are produced by species of the genus *Leishmania*, and

Table VI.11. Diseases of Man Caused by the TRYPANOSOMIDAE

DISEASE	ETIOLOGIC AGENT
Kala azar	*Leishmania donovani*
Oriental sore	*L tropica*
Mucocutaneous leishmaniasis	*L brasiliensis*
Trypanosomiasis West Africa	*Trypanosoma gambiense*
Trypanosomiasis, East Africa	*T rhodesiense*
Chagas' disease	*T cruzi*

the remainder are caused by members of the genus *Trypanosoma* (Table VI 11)

All species listed in the above table have both vertebrate and invertebrate hosts Their life cycles are carried on partly in certain insects and partly in man or other mammals, the parasites living alternately in the blood or other tissues of the vertebrate and in the gut of the insect The leishmanial parasites all occur as intracellular organisms, principally in cells of the reticuloendothelial system The trypanosomes, on the other

ro

iro-

m

Table VI.12. Stages in Life Cycles of the TRYPANOSOMIDAE of Man‡

SPECIES OF PARASITE	STAGE IN MAN	STAGE IN INSECT	STATION
Leishmania donovani	*Leishmanial	Leptomonad	A**
L tropica	*Leishmanial	Leptomonad	A
L brasiliensis	*Leishmanial	Leptomonad	A
Trypanosoma gambiense	*Trypanosomal	Crithidial trypanosomal	A
T rhodesiense	*Trypanosomal	Crithidial, trypanosomal	A
T cruzi	*Leishmanial, crithidial (?) trypanosomal	Crithidial, trypanosomal	P†

* = the multiplicative stage in man
** A = anterior station
† P = posterior station
‡ See p 391 for discussion of *T rangeli*

Developmental Stages. In the course of the life cycle in the invertebrate and the vertebrate hosts multiplication occurs and certain members of the family pass through developmental stages in which they resemble other genera within the family (Fig VI 45).

In the *leishmanial stage* the parasite is an intracellular organism which

of the parasite (Fig VI 45).

The *leptomonad stage* occurs in the life cycle of members of the genus *Leishmania* in the insect host and in culture It has not been found in

little resemblance to lung tissue since the alveolar septa are so widened by cellular infiltration that many of them press against each other thus presenting a fairly solid and markedly cellular appearance Alveolar spaces may be obliterated completely The alveolar ducts likewise are compressed or filled with exudate Pathologically this disease is characterized by a diffuse interstitial pulmonary infiltration by mononuclear cells which for the most part resemble plasma cells An alveolar exudate is present and contains a foamy or honeycombed material in which *P carinii* may be found The parasites are extracellular

Clinical Characteristics This disease is remarkable clinically in presenting almost no symptoms until late in its course in showing marked predilection for premature or immature infants and for being confined usually to infants from six weeks to four months old The onset is insidious Clinical diagnosis is based chiefly on a gradual onset with increasing tachypnea dyspnea and cyanosis Fever and cough are absent unless aspiration pneumonia develops The respiratory rate in advanced cases is from 90 to 120 per minute Physical examination may reveal areas of fine crepitant rales X ray examination reveals a picture of consolidation atelectasis and emphysema The total leukocyte count and the erythrocyte sedimentation rate are variable The duration of the clinical manifestations is two to three weeks Frequently the mild initial stage is overlooked and the illness is not apparent until a few days before death The mortality ranges from 15 to 60 per cent with death most often due to asphyxia

Diagnosis Routine chest films and respiratory rate counts are the measures of greatest value for early detection of infection in exposed patients in hospital wards when the infection is present At autopsy the best method of diagnosis is by Giemsa stained smears of the alveolar exudate of lung tissue and demonstration of *P carinii*

Treatment Only supportive measures especially oxygen with rest and constant nursing care are of benefit The infection has not responded to antibiotics antimalarials or other protozoacidal drugs

38

The Trypanosomidae

Introduction
only members c
man or animals
flagellates Three are produced by species of the genus *Leishmania* ...

Table VI.11. Diseases of Man Caused by the TRYPANOSOMIDAE

DISEASE	ETIOLOGIC AGENT
Kala azar	*Leishmania donovani*
Oriental sore	*L tropica*
Mucocutaneous leishmaniasis	*L brasiliensis*
Trypanosomiasis, West Africa	*Trypanosoma gambiense*
Trypanosomiasis East Africa	*T rhodesiense*
Chagas' disease	*T cruzi*

the remainder are caused by members of the genus *Trypanosoma* (Table VI 11)

All species listed in the above table have both vertebrate and invertebrate hosts Their life cycles are carried on partly in certain insects and partly in man or other mammals, the parasites living alternately in the blood or other tissues of the vertebrate and in the gut of the insect The leishmanial parasites all occur as intracellular organisms, principally in cells of the reticuloendothelial system The trypanosomes, on the other hand, are extracellular parasites occurring in the blood, lymph or cerebrospinal fluid *Trypanosoma cruzi* is the only member of the family producing both trypanosomal forms in the blood and leishmanial stages in the tissue cells of man (Table VI 12)

Table VI.12. Stages in Life Cycles of the TRYPANOSOMIDAE of Man‡

SPECIES OF PARASITE	STAGE IN MAN	STAGE IN INSECT	STATION
Leishmania donovani	*Leishmanial	Leptomonad	A**
L tropica	*Leishmanial	Leptomonad	A
L brasiliensis	*Leishmanial	Leptomonad	A
Trypanosoma gambiense	*Trypanosomal	Crithidial trypanosomal	A
T rhodesiense	*Trypanosomal	Crithidial, trypanosomal	A
T cruzi	*Leishmanial, crithidial (?) trypanosomal	Crithidial, trypanosomal	P†

* = the multiplicative stage in man
** A = anterior station
† P = posterior station
‡ See p 391 for discussion of *T rangeli*

Developmental Stages. In the course of the life cycle in the invertebrate and the vertebrate hosts multiplication occurs and certain members of the family pass through developmental stages in which they resemble other genera within the family (Fig. VI 45)

In the *leishmanial stage* the parasite is an intracellular organism which occurs only in the mammal It is a nonflagellated round or ovoid body measuring 1 5 to 5 μ in greatest diameter and containing a spherical vesicular nucleus and a smaller kinetoplast complex Occasionally a fibril, the rhizoplast, may be seen extending from the kinetoplast to the periphery of the parasite (Fig VI 45).

The *leptomonad stage* occurs in the life cycle of members of the genus *Leishmania* in the insect host and in culture It has not been found in

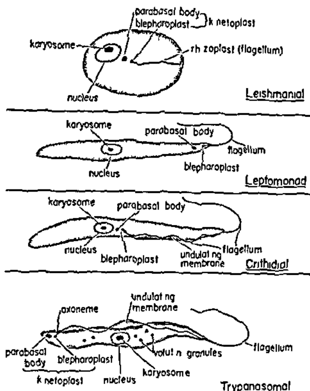


Figure VI 45 Leishmanial, leptomonad crithidial, trypanosomal forms of the TRYPANOSOMIDAE.

man *The leptomonad form is slender and elongate with a centrally* placed vesicular nucleus A single anterior flagellum arises from a well developed kinetoplast near the anterior extremity of the body There is *no undulating membrane*

The *crithidial stage* occurs in the course of the life cycle of members of the genus *Trypanosoma* Crithidia usually occur in the insect vector where multiplication occurs The typically slender crithidial form resembles the leptomonad in general contour The vesicular nucleus is centrally placed The kinetoplast is situated near and anterior to the nucleus The single flagellum continues as the free border of a short undulating membrane which extends to the anterior extremity of the parasite At this point the flagellum becomes free

The *trypanosomal stage* occurs only among members of the genus *Trypanosoma* It is represented by a metacyclic phase and a mature phase The metacyclic form is the young infective trypanosome which develops only in the insect vector It represents the culmination of the reproductive crithidial stage, which is not infective to the mammal When the metacyclic trypanosome is found in the salivary glands of the insect it is said to have an anterior station When it is developed in the hind gut and is passed in the feces the term posterior station is used The metacyclic trypanosome has a relatively short stumpy body with a

centrally placed nucleus The kinetoplast is situated posterior to the nucleus The single flagellum forms the border of an undulating mem brane which extends along the greater portion of the body of the para site becoming free at the anterior extremity The mature trypanosome is longer and more slender The nucleus is usually centrally placed The kinetoplast is situated near the posterior extremity Volutin granules are scattered through the cytoplasm Two forms of mature trypanosomes may be encountered In the monomorphic type all individuals are mor phologically similar each possessing a central nucleus a posteriorly placed kinetoplast a long undulating membrane and a long anterior flagellum Those of the polymorphic type on the other hand exhibit morphologic differences particularly with respect to variation in size position of the nucleus and length of the flagellum Locomotion of the trypanosome is usually in the direction of the free flagellum

Multiplication of the parasites in these genera occurs by longitudinal fission Division of the blepharoplast the parabasal body and the nu cleus precedes division of the cytoplasm The flagellum when present does not divide but as division of the blepharoplast occurs a new flagellum rapidly develops while the old flagellum persists With fission of the cytoplasm two separate flagellated organisms are produced

The diagnosis of leishmanial and trypanosomal infections in man is based upon demonstration of the parasites in stained smears of blood spinal fluid material aspirated from cutaneous lesions lymph nodes bone marrow or spleen or in fixed and stained tissue sections The

fication of *T cru i* infections an uninfected reduviid bug is allowed to feed upon the infected individual and subsequently the trypanosomes may be demonstrated in its feces

When stained with the Romanowsky or common tissue stains the cytoplasm of these parasites appears blue the nucleus pink and the kinetoplast a deep red

Dogs cats monkeys mice rats guinea pigs Chinese and European hamsters the gerbil and certain species of squirrels have all been shown to be susceptible in varying degree to infection by species of *Leishmania* The hamster is one of the best experimental animals

39

Leishmaniasis

Revised by Harry Most

The term leishmaniasis includes a variety of conditions which may conveniently be subdivided into visceral and superficial infections These diseases are produced by protozoal parasites belonging to the genus *Leishmania* Although the different organisms are morphologically identical, they are classified as different species within the genus (Table VI 13)

The leishmania localize in the reticuloendothelial cells of the viscera or the skin Thus in kala-azar the pathologic changes occur predominantly in the spleen, liver and bone marrow In postkala azar dermal leishmaniasis the localization of the parasites is more widely distributed throughout the skin of the body In oriental sore, on the other hand, only the exposed skin areas are affected The Central and South American form of leishmaniasis likewise involves exposed skin areas, and there is invasion of the mucous membranes of the nose, mouth and pharynx as well

Oriental sore occurs as a natural disease of dogs Human and canine infections are frequently found to be endemic in the same area and the lesions in the dog do not differ from those in man Several other mammalian species are susceptible Animals which have recovered from oriental sore have a solid immunity against reinfection by *L tropica* They are not immune, however, to *L donovani*, the etiologic agent of kala-azar On the other hand, infection by *L donovani* confers immunity both to this parasite and to *L tropica* Such evidence suggests that these parasites although related, are not identical This is further supported by the distinctly different geographic distribution of oriental sore and kala-azar (Fig VI 46)

Table VI.13. Human Leishmaniasis

TYPE	COMMON NAME	ETIOLOGIC AGENT
Visceral	Kala-azar (Indian and Oriental)	*Leishmania donovani*
	Kala-azar (Mediterranean)	*L donovani*
Dermal	*Postkala azar dermal leishmaniasis*	*L donovani*
Cutaneous	Oriental sore	*L tropica*
Naso-oral	Mucocutaneous leishmaniasis	*L brasiliensis*

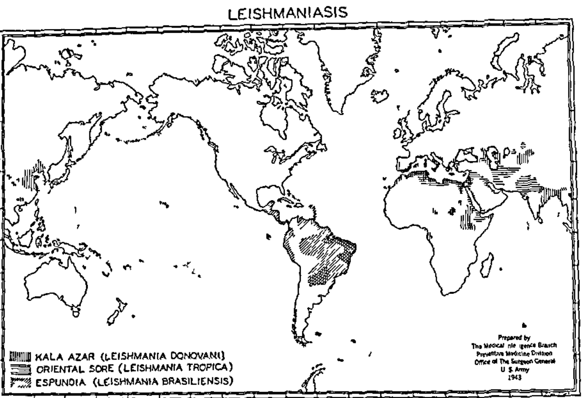


Figure VI 48 Geographic distribution of leishmaniasis

39

Leishmaniasis

Revised by Harry Most

The term leishmaniasis includes a variety of conditions which may conveniently be subdivided into visceral and superficial infections These diseases are produced by protozoal parasites belonging to the genus *Leishmania* Although the different organisms are morphologically identical, they are classified as different species within the genus (Table VI 13)

The leishmania *localize in the reticuloendothelial cells of the viscera* or the skin Thus in kala azar the pathologic changes occur predominantly in the spleen, liver and bone marrow In postkala azar dermal leishmaniasis the localization of the parasites is more widely distributed throughout the skin of the body In oriental sore, on the other hand, only the exposed skin areas are affected The Central and South American form of leishmaniasis likewise involves exposed skin areas, and there is invasion of the mucous membranes of the nose, mouth and pharynx as well

Oriental sore occurs as a natural disease of dogs Human and canine infections are frequently found to be endemic in the same area and the *lesions in the dog do not differ from those in man Several other mam*malian species are susceptible Animals which have recovered from oriental sore have a solid immunity against reinfection by *L tropica* They are not immune, however, to *L donovani*, the etiologic agent of

parasites and g .
by the distinctly different geographic distribution of oriental sore and kala azar (Fig VI 46)

Table VI.13. Human Leishmaniasis

TYPE	COMMON NAME	ETIOLOGIC AGENT
Visceral	Kala azar (Indian and Oriental)	*Leishmania donovani*
	Kala azar (Mediterranean)	*L donovani*
Dermal	Postkala azar dermal leishmaniasis	*L donovani*
Cutaneous	Oriental sore	*L tropica*
Naso-oral	Mucocutaneous leishmaniasis	*L brasiliensis*

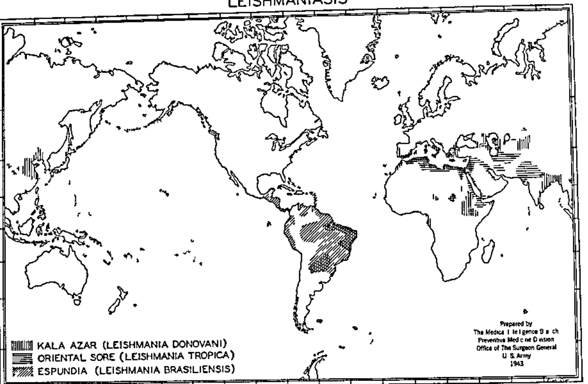


Figure VI 46 Geographic distribution of leishmaniasis

Table VI.14. Known and Probable Vectors of Leishmaniasis

Leishmania donovani Kala-azar	
Asia India, China, Pakistan	* *Phlebotomus argentipes* * *P. chinensis* * *P sergenti* var *mongolensis*
Middle East Israel, Turkey	*P perfiliewi* * *P papatasii*
Mediterranean Greece, Sicily, Italy, Spain, Cyprus, Portugal	* *P perniciosus* *P major* * *P. papatasii* * *P tobbi* * *P chinensis* * *P perfiliewi* *P vesuvianus*
North Africa Sudan, Ethiopia, Algeria	*P sergenti* *P orientalis* * *P perniciosus* * *P longicuspis*
South America Brazil, Venezuela, Argentina, Paraguay, Bolivia	*P intermedius* (= *lutzi*) * *P longipalpis* * *P panamensis*
Leishmania tropica Cutaneous Leishmaniasis	
Asia Middle Asia (U S S R) Turkmenistan (only rodents), Iran	* *P papatasii* * *P caucasicus*
Mediterranean Israel, Turkey, Italy, Syria	*P caucasicus* * *P perfiliewi*
Africa Algeria, Tunisia, Libya, Egypt, central Africa	* *P sergenti* † *Stomoxys calcitrans*
Leishmania brasiliensis Mucocutaneous Leishmaniasis	
Central and South America Brazil, Peru, Venezuela	* *P intermedius* (= *lutzi*) ‡ *P migonei* *P evansi* ‡ *P whitmani* *P gomezi* ‡ *P pessoai* *P paraensis* *P. squamiventris* ‡ *P fischeri* (experimental) *P verrucarum* *P peruensis*

* Vectorship generally accepted by most authors, in regard to all others there is a difference of opinion In many cases evidence is epidemiologic only
† Mechanical transmission—experimentally
‡ Only to monkeys—experimentally

The various leishmaniases have essentially the same epidemiology Several species of biting flies belonging to the genus *Phlebotomus* are chiefly responsible for the transmission of the parasites (Table VI 14) These flies are small and hairy They are weak fliers remaining near the ground and in close proximity to the breeding area Their larvae develop in cracks in masonry and walls and in rubbish and stone piles

Man the dog wild rodents and possibly other mammals serve as endemic reservoirs for species of *Leishmania* in various parts of the world *Phlebotomus* flies acquire the protozoan by direct ingestion from the infected skin or from parasites present in the ingested blood of the reservoir host Leishmanial organisms after entrance into the insect s gut develop into leptomonad flagellates undergo multiplication and ultimately come to occupy an anterior station in the insect s pharynx It is believed that when the flies subsequently feed on man these leptomonad forms gain access to the human body localizing in the cells of the reticuloendothelial system where they undergo extensive multiplication as leishmanial forms

40

Kala-Azar

Revised by Harry Most

Synonyms Dumdum fever tropical splenomegaly black sickness splenic anemia of infants ponos

Definition Kala azar is a disease produced by a protozoal organism *Leishmania donovani* It is characterized by irregular fever of long duration chronicity enlargement of the spleen and often of the liver emaciation anemia leukopenia and hyperglobulinuria

Distribution Kala azar is widely distributed in certain portions of

central Asia

EUROPE It is present in southern Russia Transcaucasia Turkestan and the Mediterranean littoral including southern Italy France Spain and the Mediterranean islands

AFRICA It is present in Morocco Algeria Tunis Tripolitania Cyrenaica Egypt Sudan Kenya Equatorial Africa and Nigeria

WESTERN HEMISPHERE Visceral leishmaniasis or kala azar occurs in Paraguay Argentina and Brazil

INFANTILE KALA AZAR Infantile kala azar is limited in its geographic distribution to the Mediterranean basin Portugal Spain southern France Turkey Yugoslavia and Hungary

Etiology Kala azar of India and the Orient and the disease in children in the Mediterranean area were formerly considered to be caused by two different parasites *L donovani* and *L infantum* but *L donovani* is now accepted as the etiologic agent of both diseases *This is a round or ovoid* organism measuring 2 to 5 μ in diameter containing a relatively large and peripherally placed vesicular nucleus A rod shaped or proximity to it tc the rhizoplast m to the periphery

When stained with a Romanowsky stain the cytoplasm appears faintly blue and the nucleus and kinetoplast are red or reddish purple

The leishmania or Leishman Donovan bodies are found within cells of the reticuloendothelial system monocytes polymorphonuclear neutrophils and other phagocytic cells

Epidemiology In both India and China kala azar is a rural disease occurring principally in low alluvial plains It rarely occurs at altitudes in excess of 2000 feet There are three factors essential for transmission—a reservoir of infection a suitable vector and a susceptible population Susceptibility of the population appears to be highly important Recovery from infection is accompanied by relatively complete immunity of long duration Under endemic conditions the disease chiefly affects children It appears to become epidemic only when the general resistance of the population is lowered Adults then are affected with increasing frequency Kala azar occurs in both sexes at all ages It is a disease primarily of the poorer classes Epidemics have been restricted principally to India (Fig VI 47)

In most areas where the leishmanial diseases are endemic it is probable that infected man particularly in the case of postkala azar dermal leishmaniasis constitutes the most important reservoir In the Mediterranean region however infected dogs are believed to be reservoirs for the infantile form of the disease In China also cutaneous leishmaniasis of dogs is not uncommon and naturally infected *dogs have been found* in Brazil These animals however are not found infected in India and presumably play no part in the epidemiology of Indian kala azar *Phlebotomus sergenti* var *mongolensis* and *P chinensis* in China and certain of the Brazilian and Paraguayan species have been shown to acquire infection from these animals

The *sandfly vectors* (various species of *Phlebotomus*) are weak fliers and are most numerous in the immediate proximity of the breeding places For the most part, they remain close to the ground and consequently are much less numerous above the first floor in houses They breed in cracks in the walls and masonry and in collections of rubbish

and rubble Tl e average life of the sandfly is estimated to be 14 to 16 days *Phlebotomus argentıj es* ıs cons dered the most ımportant vector ın India and *P cl nensıs* ın Ch na

Le shman al bod es present ın tl e per pheral blood ın the course of tl e active d sease are ingested by tl e vector Leptomonad forms may be observed ın the gut of the insect by the th rd day after the infective blood meal They move forward to occupy an anterıor station ın the

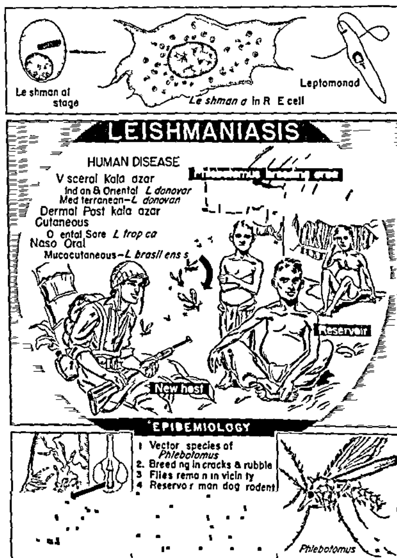


Figure VI.47 Ep demiology of leishmaniasis

pharynx and mouth parts by the fourth or fifth day From the seventh *to the ninth day the flagellates often invade the proboscis* and the flies are then infective The organisms are presumed to enter the new host during subsequent biting Successful transmission by the sandfly to *hamsters and to man has been accomplished*

Leishmanial bodies have been demonstrated in the urine and feces of infected humans They have also been found in material obtained by swabbing the nasal mucosa and the tonsil and have been demonstrated in the saliva of infected individuals This implies the possibility of direct man to man transmission by droplet infection It seems probable, however that this method of spread if it occurs is of minor importance because of the sharp geographic limitations the failure of the disease to extend outside these regions and its absence at altitudes above 2000 feet within the endemic areas

Animals have been shown to acquire leishmaniasis by eating infected carcasses It is possible that this may be a factor in maintaining the animal reservoir

Pathology The chief lesion of kala azar is essentially a marked hyperplasia of the cells of the reticuloendothelial system particularly of the spleen and liver The leishmania multiply within these cells which ultimately rupture releasing the parasites which are then taken up by other reticuloendothelial cells They are ingested to a lesser extent by leukocytes and monocytes which occasionally may be found containing leishmania in films of the peripheral blood

The spleen may be greatly enlarged owing principally to the enormous increase of reticuloendothelial cells many of which are parasitized

The liver is usually but not always enlarged in kala azar There is marked proliferation of the Kupffer cells which contain large numbers of leishmanial bodies Pressure atrophy of the liver cords occurs and both cloudy swelling and fatty degeneration may be observed In advanced chronic cases there may be some fibrosis of the parenchyma *(Fig VI 49)*

The villi of the small intestine especially the duodenum and jejunum may be crowded with parasitized reticuloendothelial cells and ulceration of the overlying mucosa occasionally occurs Less often similar lesions are reported in the colon and rarely cells containing parasites may be observed in the mucous membrane of the stomach

In the bone marrow there is a progressive replacement of the hematopoietic tissue and the fatty marrow by masses of heavily parasitized reticuloendothelial cells In experimental infections of animals amyloid disease of the kidneys may be found and it is probable that similar changes occur in human infections

There are no characteristic lesions of other organs Scattered infected phagocytic cells may be observed The lymph nodes are often enlarged owing to obstruction of the lymph sinuses by parasitized reticulo endothelial cells

ppear until some
In the Sudan it
early lesions are
meter, occurring
particularly on the face, neck, the extensor surface of the forearms and the inner aspect of the thighs There is little change in the epidermis,

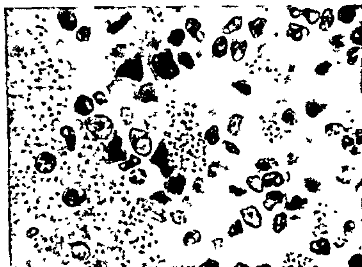


Figure VI.48 Parasitized reticuloendothelial cells in splenic pulp in *Leishmania donovani* infection. (Courtesy of the Louisiana State University School of Medicine)

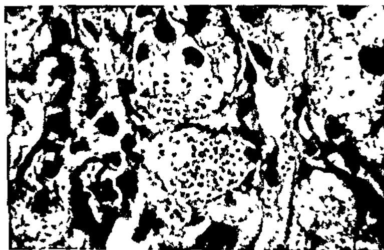


Figure VI 49 Kala-azar biopsy of liver showing *L. donovani* (Tissue section courtesy of Dr J Rodrigues da Silva Rio de Janeiro photomicrograph courtesy of Louisiana State University School of Medicine)

but the pigment in the basal layer is diminished The subpapillary layer is edematous the vessels are dilated, and there is infiltration by macrophage cells Parasites are scanty

A second type of skin lesion, nodular in character, likewise occurs in postkala azar dermal leishmaniasis In this type there is a thinning of the epidermis over a nodular granulomatous mass of reticuloendothelial cells, some of which contain leishmanial bodies This condition sometimes develops after inadequate therapy of visceral leishmaniasis with antimony

Less commonly xanthomatous lesions of the skin are observed In these there is a marked increase of connective tissue Parasites are rare

Clinical Characteristics The duration of the incubation period is not known exactly It is usually considered to be two to four months rarely it may be only ten to 14 days

The onset may be sudden or gradual In some instances it is acute, accompanied by chills high fever and vomiting In others it resembles typhoid and is characterized by general malaise and rising fever, which reaches 103° to 104° F in about a week In still others it is insidious slow and unaccompanied by any significant febrile reaction

During the acute stage the fever is frequently intermittent with two daily remissions, and each drop in temperature is often accompanied by profuse sweating Chara
the early afternoon subsi
before midnight This type
monly It may be observed
The initial fever may last two to six weeks Thereafter if the disease becomes chronic, it is characterized by recurring febrile waves resembling those observed in brucellosis

The first noticeable enlargement of the spleen may occur as late as five months after the onset of the acute phase although it is usually at or below the costal margin by the end of the first month In the early stages of the disease it has a doughy consistency Each wave of fever is accompanied by further enlargement followed by some reduction in size during the apyrexial periods In chronic cases the spleen is often hard and greatly enlarged, extending to the umbilicus or even to the anterior superior spine of the ilium (Fig VI 50) Soft enlargement of the liver is usually evident after the first month

Diarrhea and at times even dysentery are not uncommon during the acute stage As the disease progresses there is marked emaciation most noticeable in the limbs and the chest wall Drenching night sweats are common Despite these symptoms and the height of the fever curve toxemia is inconspicuous The appetite usually remains good and the tongue clean

As the disease advances a characteristic grayish color of the skin develops from which the synonym "black disease" is derived This pigmentation is most noticeable on the hands, the nails the forehead and the central line of the abdomen

The replacement of hematopoietic marrow by parasitized reticuloendothelial cells is probably responsible for the characteristic changes

in the blood There is a leukopenia with a relative increase of lympho cytes and monocytes Although anemia is usual the red blood cells seldom fall below two and one half million and more commonly range between three and four million per cubic millimeter The erythrocytes are frequently macrocytic and hyperchromic

Progressive alteration of the plasma proteins occurs early in the dis ease The serum euglobulin is three to 13 times normal and may con stitute 30 to 63 per cent of the total serum globulins There is an abso lute decrease in the serum albumin In the late stages of the disease these changes in the plasma proteins commonly lead to ascites and edema

Purpura gingivitis stomatitis and trophic changes of the hair are common It is probable that they are to be attributed at least in part to nutritional deficiencies Pneumonia cancrum oris or intercurrent dis ease are frequent terminal phenomena

Diagnosis In endemic areas the diagnosis of kala azar may be made with reasonable assurance on clinical grounds by about the fourth month when the characteristic features splenomegaly hepatomegaly and leukopenia usually below 4000 per cubic millimeter are ordinarily well established The serum tests provide additional but not conclusive evidence In early cases the characteristic fever curve may be the only significant clinical finding

Definitive Diagnosis This depends upon the demonstration of *L donovani* in the blood or other tissues and may be accomplished by microscopic examination of stained smears by cultures or by inocula tion into hamsters

STERNAL PUNCTURE Leishmania may be demonstrated in stained smears of sternal marrow in approximately 80 per cent of the cases The

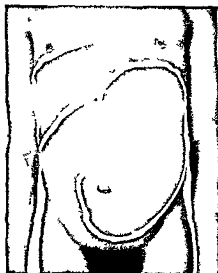


Figure VI.50 Chronic kala-azar extreme splenomegaly and hepatomegaly

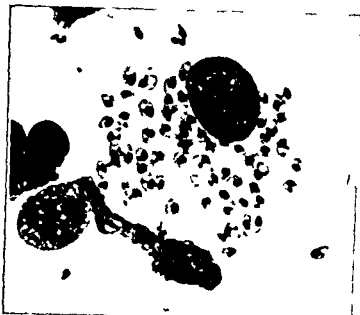


Figure VI 51 *Leishmania donovani in stained smear from spleen puncture*

parasites however are usually much less numerous than in smears of spleen pulp Culture will frequently yield positive results

LIVER PUNCTURE Needle biopsy of the liver is less hazardous than splenic puncture Leishmania may be detected in about 66 per cent of the cases at liver biopsy

SPLEEN PUNCTURE In 90 per cent of the cases leishmania will be found in stained smears of the splenic aspirate (Fig VI 51) Inoculations of N N N medium usually yield positive cultures Properly executed splenic punctures in areas where this disease is endemic have not proved to be hazardous

BLOOD CULTURE Inoculation of the sedimented cells from citrated blood into N N N medium

BLOOD SMEARS Careful examination of the leukocytes and monocytes in stained blood films may reveal leishmania in some of the cases

Serologic Diagnosis The serum tests for kala azar are based upon the increase of the euglobulin fraction When positive they provide suggestive but not conclusive evidence

COMPLEMENT FIXATION TEST A very promising complement fixation test using an antigen prepared from human tubercle bacilli has been developed Positive reaction is obtained in approximately 90 per cent of cases as early as the third week of the disease A negative reaction is obtained in all conditions entering into the differential diagnosis with the exception of about 10 per cent of cases of clinically obvious chronic pulmonary tuberculosis

Differential Diagnosis The clinical picture of kala azar frequently may resemble that produced by other diseases which occur in the endemic areas The early acute stage may be confused with malaria and in the early weeks it may also resemble atypical typhoid fever In the chronic stage it may be confused with tuberculosis brucellosis infectious mononucleosis leukemia or other hematologic disorders Infantile kala azar has been confused with Banti s disease The onset of kala azar in children is frequently insidious The clinical course is associated with splenomegaly anemia and general lymphadenitis The lesions of post

[illegible]

T[illegible] e

[illegible]

tions and significantly affects the prognosis Patients with severe disease should be hospitalized whenever it is possible

A diet high in protein and vitamin content is essential Oral hygiene is of great importance because of the frequency of the highly fatal complication cancrum oris Likewise respiratory infections must be guarded against because of the susceptibility of kala azar patients to pneumonia The presence or absence of pulmonary tuberculosis must be determined prior to the institution of therapy so that if necessary antituberculous drugs may be given simultaneously with specific antimony therapy

Specific Treatment The susceptibility of kala azar to specific drug treatment appears to vary considerably between different geographic areas The disease in India seems to be most easily cured The Chinese and Mediterranean forms occupy intermediate positions and visceral leishmaniasis of the Sudan is notoriously resistant Prior to the introduction of the currently used drugs the mortality was 95 per cent it is now 2 to 5 per cent

Two groups of compounds are recommended pentavalent organic antimonials and certain aromatic diamidines One or more of these will meet the requirements of almost all cases

PENTAVALENT ORGANIC ANTIMONIALS 1 *Sodium antimony gluconate* Synonyms Pentostam, Bayer 561 Solustibosan This drug has been widely used and found to be effective in resistant forms of the disease Toxic effects are rare It should be given daily for 15 to 20 days intravenously in 5 per cent solution for adults and intramuscularly in 25 per cent solution for children The individual injection must be a *freshly prepared* solution in sterile distilled water

The initial dose for adults is 0 2 gram subsequent doses 0 3 gram The adult dose may be used for children weighing 30 kg or more

A preparation of sodium antimony gluconate issued under the name of Pentostam is distributed in a form suitable for immediate injection It may be administered intravenously or intramuscularly The recommended adult dose is one intravenous injection of 6 ml daily for six days

2 *Neostibosan* Synonym Bayer 693 Neostibosan is a phenylstibonic acid derivative The methods of administration and dosage are the same as for sodium antimony gluconate except that this preparation should not be given intramuscularly

3 *Urea stibamine* The drug is a mixture of compounds of phenyl stibonic acid It has been widely used in India where it has proved effective It has greater toxicity than Neostibosan and should be administered by the intravenous route only since it is too irritating to give by intramuscular injection It should be given on alternate days or every third day in 5 to 10 ml of sterile distilled water It must not be heated

The initial recommended dose for an adult is 0 05 gram the second 0.1 gram the third 0 15 gram and the fourth and subsequent doses 0 2 gram

The mode of action of antimony on the leishmania is not known The parasites may continue to be present and viable on culture during at least part of the course of treatment and even for a short period after completion of therapy

The antimonyl tartrates no longer have a place in the treatment of kala azar

AROMATIC DIAMIDINES The aromatic diamidines are the most powerful known drugs for the treatment of kala azar Particularly when given intravenously reactions of some degree occur in a considerable proportion of patients These include headache flushing faintness epigastric pain and vomiting collapse and unconsciousness There is an associated fall in blood pressure and at times lowering of the blood sugar These reactions can be prevented largely or controlled by intramuscular injection of 0 25 ml of 1/1000 epinephrine or an antihistaminic immediately prior to administration of the drug

1 *Pentamidine isethionate* Synonym M&B 800 Lomidine This may be given intravenously or intramuscularly The latter route is preferred *since it is rarely associated with any of the symptoms referable to the* depressor action of the drug It should be given daily or on alternate days to a total of 12 to 15 injections Only freshly prepared solutions in sterile distilled water should be used

For intramuscular injection the dose is 4 mgm per kilogram of body weight in 3 ml of sterile distilled water for intravenous injection 2 to 4 mgm per kilogram of body weight dissolved in 5 to 10 ml of sterile distilled water

2 *Stilbamidine isethionate Stilbamidine is the most effective drug for* the treatment of kala azar but should *not* be used for routine treatment Solutions of the drug are unstable when exposed to light and unless freshly prepared cause immediate toxic reactions It is frequently followed by a late and troublesome complication "diamidino stilbene *neuropathy*" of the trigeminal nerve Use of this preparation should be restricted to antimony resistant cases

Stilbamidine must be administered intravenously and slowly in a *freshly prepared* 1 p [illegible] ter It should be given daily A m [illegible] drug per 45 kilograms of [illegible] rsons and children are relatively tolerant of the drug

No total individual dose should exceed 2 mgm per kilogram of body weight The initial dose for an adult irrespective of weight should be 0 025 gram The subsequent doses should be increased by increments

of 0 01 to 0 02 gram to a total individual dose of 2 mgm per kilogram of body weight

Experimental Therapy Amphotericin B, and its more soluble form, [illegible] maniasis in experi- [illegible] noteworthy [illegible] of antibiotic drugs and blood transfusions have greatly reduced the mortality from cancrum oris and pneumonia

Favorable response to treatment consists of definite subjective im- [illegible]

spleen, and improvement in the erythrocyte count becoming evident about a week after completion of the course of therapy

Postkala azar dermal leishmaniasis usually responds better to penta valent antimony compounds than to the aromatic diamidines The dosage recommended for the visceral infections should be used, but the injections should be spaced two or more days apart

Relapses in kala azar are not uncommon if insufficient treatment has been given The relapse is usually accompanied by fever and progressive enlargement of the spleen

Prognosis. The serious prognosis which attends untreated or incompletely treated patients necessitates long continued observation of the patient in the post treatment period The criteria of cure may be stated as complete cessation of fever for a period of several months, gain in weight, disappearance of splenomegaly, restoration of normal white blood cell and differential counts and disappearance of the anemia

Certain patients fail to respond to medical treatment despite repeated courses and adequate dosage of the various recommended drugs In such instances it is justifiable to consider splenectomy before undertaking further treatment

Prophylaxis. There are no specific prophylactic measures for kala-azar The basic problem centers around the control of the species of *Phlebotomus* which act as vectors Insect repellents furnish temporary protection for the individual However, DDT and other residual in-

41

Cutaneous Leishmaniasis

Revised by Harry Most

Synonyms Oriental sore Aleppo Bagdad or Delhi boil bouton d Orient, bouton de Biskra chiclero ulcer, forest yaws

Distribution *Oriental sore is prevalent in many tropical and sub tropical regions in both the Eastern and Western Hemispheres Its distribution, however, does not coincide with that of visceral leish maniasis (kala azar)*

ASIA Prevalent in parts of China In Asia Minor especially preva lent in Syria, Arabia Persia Israel Iraq *Iran the Caucasus southeast* U S S R, Turkestan, Pakistan

EUROPE In the Mediterranean littoral in the Mediterranean islands southern Italy, Spain the south of France and Greece

AFRICA Morocco Tunisia Algeria, Ethiopia the Sudan French Congo Lake Chad area Nigeria and on the west coast south as far as Angola

WESTERN HEMISPHERE Reported from every country in Central and *South America except Chile*

Etiology The etiologic agent of oriental sore or cutaneous leish maniasis is *Leishmania tropica* It is morphologically identical with *L donovani* and *L brasiliensis*

Epidemiology Experimental and epidemiologic evidence indicates that sandflies are natural vectors of the disease particularly *Phlebotomus papatasii* and *P sergenti* in the Near East and *P macedonicum* in Italy Successful inoculation of man by the bite of *P papatasii* has been ac complished *In Central and South America P intermedius is generally* regarded as a vector and several other species may be concerned In central Asia the gerbil a rodent is an important reservoir Although infection by *L tropica* occurs by direct inoculation the parasites do not penetrate the unbroken skin

Cutaneous leishmaniasis may occur in almost epidemic form Chil dren are more commonly affected than adults There is no distinctive sex incidence A fairly solid immunity follows infection in man This

scar will be least disfiguring

Pathology Following inoculation of the skin either through the bite of an infected sandfly or by some other means a nodule develops that is produced by infiltration of the corium with plasma cells lymphocytes and large endothelial macrophages Thinning and atrophy of the overlying epidermis often occur Perivascular infiltration then becomes prominent and polymorphonuclear leukocytes more numerous Focal accumulations of endothelial phagocytes filled with leishmania are seen (Fig VI 52)

With further progression an ulcer develops that has a granulation tissue base and a surrounding zone of inflammation Infiltration extends into the subcutaneous connective tissue in which reticuloendothelial cells plasma cells and lymphocytes are prominent. Occasional giant cells are present

The leishmania are often difficult to demonstrate in the fully developed ulcer and may be found only at the margin of the lesion or in scrapings from its floor There is no general dissemination of the parasites Ultimately the leishmania disappear granulation tissue becomes more abundant and healing occurs leaving a depressed fibrous scar (Fig VI 53)

Clinical Characteristics The incubation period of oriental sore may vary from a few weeks to several months The lesions may be multiple They appear first as slowly growing papules on an exposed skin area As ulceration develops they become covered with a crust which exudes a sticky secretion On removal of the crusts moist freely bleeding ulcers are revealed These ulcers are usually not deep and ordinarily vary from 1 to 3 cm in diameter Secondary infection is usual and when severe greater tissue destruction may result After effective treatment

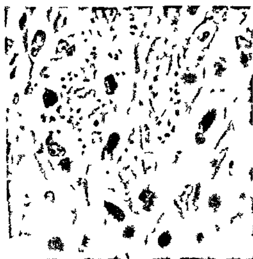


Figure VI.52. Section through the indurated edge of oriental sore showing cellular infiltration including heavily parasitized reticuloendothelial cells. (Courtesy of Dr H. Most, New York University School of Medicine)

41

Cutaneous Leishmaniasis

Revised by Harry Most

Synonyms. Oriental sore, Aleppo, Bagdad, or Delhi boil, bouton d'Orient, bouton de Biskra, chiclero ulcer, forest yaws

Distribution. Oriental sore is prevalent in many tropical and subtropical regions in both the Eastern and Western Hemispheres. Its distribution, however, does not coincide with that of visceral leishmaniasis (kala-azar).

ASIA. Prevalent in parts of China. In Asia Minor, especially prevalent in Syria, Arabia, Persia, Israel, Iraq, Iran, the Caucasus, southeast U.S.S.R., Turkestan, Pakistan.

EUROPE. In the Mediterranean littoral, in the Mediterranean islands, southern Italy, Spain, the south of France and Greece.

AFRICA. Morocco, Tunisia, Algeria, Ethiopia, the Sudan, French Congo, Lake Chad area, Nigeria and on the west coast south as far as Angola.

WESTERN HEMISPHERE. Reported from every country in Central and South America except Chile.

Etiology. The etiologic agent of oriental sore or cutaneous leishmaniasis is *Leishmania tropica*. It is morphologically identical with *L. donovani* and *L. brasiliensis*.

Epidemiology. Experimental and epidemiologic evidence indicates that sandflies are natural vectors of the disease, particularly *Phlebotomus papatasii* and *P. sergenti* in the Near East, and *P. macedonicum* in Italy. Successful inoculation of man by the bite of *P. papatasii* has been accomplished. In Central and South America *P. intermedius* is generally regarded as a vector and several other species may be concerned. In central Asia, the gerbil, a rodent, is an important reservoir. Although infection by *L. tropica* occurs by direct inoculation, the parasites do not penetrate the unbroken skin.

Cutaneous leishmaniasis may occur in almost epidemic form. Children are more commonly affected than adults. There is no distinctive sex incidence. A fairly solid immunity follows infection in man. This has long been the basis for deliberate inoculation of children in endemic areas, the inhabitants knowing that the induced attack confers protection against naturally acquired infection. Sites are chosen where the resultant scar will be least disfiguring.

Pathology. Following inoculation of the skin either through t bite of an infected sandfly or by some other means, a nodule develop that is produced by infiltration of the corium with plasma cells, lym phocytes and large endothelial macrophages Thinning and atrophy o the overlying epidermis often occur Perivascular infiltration then be comes prominent and polymorphonuclear leukocytes more numerous Focal accumulations of endothelial phagocytes filled with leishmania are seen (Fig VI 52).

With further progression, an ulcer develops that has a granulation tissue base and a surrounding zone of inflammation Infiltration extends into the subcutaneous connective tissue in which reticuloendothelial cells, plasma cells and lymphocytes are prominent. Occasional giant cells are present

The leishmania are often difficult to demonstrate in the fully de veloped ulcer and may be found only at the margin of the lesion or in scrapings from its floor There is no general dissemination of the para sites Ultimately the leishmania disappear, granulation tissue becomes more abundant and healing occurs, leaving a depressed fibrous scar (Fig VI 53)

Clinical Characteristics. The incubation period of oriental sore may vary from a few weeks to several months The lesions may be mul tiple They appear first as slowly growing papules on an exposed skin area As ulceration develops they become covered with a crust which exudes a sticky secretion On removal of the crusts moist, freely bleeding ulcers are revealed These ulcers are usually not deep and ordinarily vary from 1 to 3 cm in diameter Secondary infection is usual and, when severe, greater tissue destruction may result After effective treatment,



2 Section through the indurated edge of oriental sore showing cellular ... luding heavily parasitized reticuloendothelial cells. (Courtesy ... k University School of Medicine.)



Figure VI 53 The extremities are favorite sites for oriental sores (Delhi boil, Aleppo boil) Beginning as a small papule the lesion becomes a plaque called 'Biskra button' (A) later the ulceration extends showing rolled indurated edges (B) Complete healing with scarring usually occurs but satellite lesions may be formed (C) with central scarred areas and secondary ulcerated nodules (Courtesy Ash and Spitz Pathology of Tropical Diseases)

or after a number of months if no treatment is given healing occurs by granulation and a lasting immunity is produced

Dry and moist types of cutaneous leishmaniasis have been described In the former the incubation period and duration of the lesions are long dry papules persist for months before ulcerating The incubation period and duration of the moist lesions are shorter they ulcerate rapidly Vaccination with either type apparently does not provide cross immunity

Diagnosis The development of one or more cutaneous ulcers on exposed skin areas of the body in a region where oriental sore is known to be endemic and where sandflies are present should arouse suspicion of this condition Definitive diagnosis depends upon the demonstration of *L tropica* obtained from the lesion Examination of the exudate will seldom be successful Smears made from curettings of the base or the sides of the ulcer should be used or a fine hypodermic needle introduced through normal skin may be inserted into the indurated margin of th lesion and material aspirated for preparation of a stained smear Unde sterile conditions material aspirated from the margin of the lesion m inoculated into N N N medium and leptomonad forms recover after incubation at 22° C (p 822) Bacterial contamination of cultu or leishmania may be prevented or controlled by the addition of p cillin and other suitable antibiotics (p 822)

The other diagnostic procedures of value in kala azar are not ap priate for oriental sore Leishmania are not found in the blood anemia leukopenia or hyperglobulinemia are not features of this tion

The differential diagnosis of cutaneous leishmaniasis must blastomycosis yaws tertiary syphilis and lupus

Treatment. The best results in all cases are obtained fo of parenterally administered Neostibosan In general

jection of lesions is undesirable because of the frequency of severe infection A total of ten or 12 injections of Neostibosan intravenously given on alternate days will cure most patients Antibiotics may be applied to the lesion to combat b icterial infection and to promote healing

42

Naso-oral or Mucocutaneous Leishmaniasis

Revised by Harry Most

Synonyms American leishmaniasis uta bubas espundia

Distribution This infection is widely distributed throughout Central and South Americ i with the exception of Chile Although a clinically similar condition has been observed in India and Afric i its identity is uncertain

s

predominantly in forest workers Men are more frequently affected than women This difference in sex incidence however is probably occupational in character It is believed on epidemiologic grounds, that various species of sandflies *Phlebotomus* are the vectors and that transmission from infected m in or animals is accomplished by the bite of these insects The spiny rats *Proechimys semispinosus panamensis* and *Hoplomys gymnurus* have been found naturally infected with *L braziliensis* in Panama The disease has occurred in epidemic form in man in Paraguay

Pathology American leishmaniasis is distinguished from oriental sore primarily by the fact that in 10 to 20 per cent of cases of "oriental

healing is often accompanied by great deformity of the affected structures The mucosae may be invaded by direct extension from an adjacent cutaneous lesion or the nasopharyngeal process may be secondary to a distant primary focus the latter in some cases having healed prior to the onset of the secondary development

The development of the lesion is similar to that of oriental sore It appears first as a small papule later becoming crusted and exuding a

ticky substance Removal of the crust reveals a freely bleeding ulcer This extends slowly into adjacent tissues increasing both in size and depth as secondary infection is established The cartilage and bony support of the nose are often destroyed and the hard and soft palate and walls of the pharynx are sometimes similarly affected Death occur from sepsis or malnutrition

Leishmania may be recovered from nodules and the indurated mar gins of ulcers There is no general dissemination although rarely they may be found in the regional lymph nodes adjacent to an active lesion

Clinical Characteristics The disease begins as a small papule appearing on an exposed skin surface often on the margins of the ears Ulcer formation follows and the process at this stage does not differ from oriental sore Later ulcers develop about the margins of the nose and mouth and may extend causing widespread destruction of tissue in the naso oral region

Diagnosis In advanced cases with extensive secondary infection it may be impossible to demonstrate leishmania Material for staining or culture should be obtained by curettage of the indurated margin of the lesion or by aspiration from this area The Montenegro intradermal test is of considerable diagnostic value

The differential diagnosis of this condition involves consideration of yaws leprosy tertiary syphilis blastomycosis lupus and nasal myiasis

Treatment The prognosis is much more serious than that of oriental sore because of the destructive mucocutaneous lesions To prevent these serious complications intensive treatment with Neostibosan intravenously should be instituted at the earliest possible mo ment Treatment should be continued until apparent cure is obtained and the patient should be observed for an additional period

Additional or subsequent treatment if required consists of the adm istration of a course of tartar emetic intravenously (see treatment schistosomiasis japonica p 513) Secondary bacterial infection must treated by the appropriate antibiotics and sulfonamides Recen Amphotericin B has been found to have therapeutic efficacy

43

African Trypanosomiasis

Synonyms Sleeping sickness maladie du sommeil (Schlafkrankheit (German)

Definition African trypanosomiasis is an acute and ch tozoal disease produced by hemoflagellates of the genus *Try* TRYPANOSOMIDAE It is transmitted by various specie

flies all of which fall in the genus *Glossina* The acute disease is distinguished by fever adenitis rash and transitory edemas The chronic form appears when the central nervous system is invaded and is characterized clinically by meningo encephalitis and meningomyelitis with wasting and mental and physical apathy which may progress into coma and death

Distribution The disease is limited to the tsetse fly areas of Africa It is endemic throughout most of the tropical area of the continent (Fig VI 54)

Etiology *Trypanosoma gambiense T rhodesiense* and *T brucei* have been regarded in the past as separate species They are morphologically identical

Trypanosoma rhodesiense is usually more virulent in man than *T gambiense*

An alternate view is that both species are primarily parasites of wild animals with the important difference that *T rhodesiense* can also infect man but that *T brucei* does not T

slender flagellates tapering to a

tively blunt posterior extremity

The trypanosomes are polymorphic some having a free flagellum and some lacking it When the parasites are present in the blood in considerable numbers both long narrow and short stumpy forms may be seen The former have a long flagellum whereas the latter have none or at most a very short one At times the nucleus may be situated posteriorly occasionally close to the kinetoplast At different stages of the disease trypanosomes may be found in the blood the lymph and the tissues of the central nervous system

Epidemiology *Reservoir* Man is an important reservoir for *T gambiense* and *T rhodesiense* It is believed that certain domestic animals notably the pig may likewise serve in this capacity particularly for *T gambiense* *T rhodesiense* has been transmitted through sheep antelope and monkeys Human volunteers have been infected by single *G morsitans* which had fed on experimentally infected sheep monkeys and several species of wild animals A strain of *T rhodesiense* has been isolated from a naturally infected wild bushbuck and transmitted to man by subinoculation this demonstrates that *T rhodesiense* can occur in wild game animals and establishes finally that Rhodesian sleeping sickness is a zoonosis

The morphologic identity of the two human trypanosomes and of *T brucei* which is widely prevalent in various antelope and ungulates has given rise to the belief that the human strains may be variants of *T brucei* and that wild game is the ultimate reservoir of infection (Fig VI 55)

so far been proven to be of importance in the epidemiology of trypanosomiasis (Table VI 15)

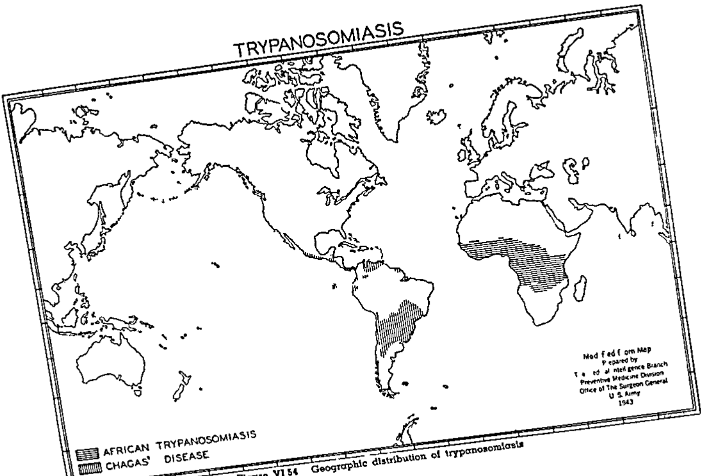


Figure VI 54 Geographic distribution of trypanosomiasis

When these trypanosomes are ingested by the fly they multiply in the midgut and hindgut Depending upon conditions of temperature and humidity long slender forms appear from the eighth to the 18th day These move anteriorly to the proventriculus then to the salivary glands and ducts where crithidial forms are produced The infective metacyclic trypanosomes which are similar to the short stumpy trypano-

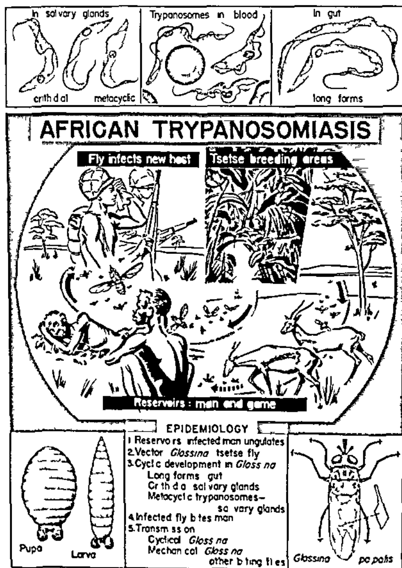


Figure VI.55 Epidemiology of African trypanosomiasis.

Table VI 15 Principal Vectors of African Trypanosomiasis

SPECIES OF *Trypanosoma*	SPECIES OF *Glossina*
T gambiense	*G palpalis**, *G tachinoides**, *G pallidipes*, *G brevipalpis*, *G fusca*
T rhodesiense	*G morsitans**, *G swynnertoni*, *G brevipalpis*
T brucei	*G morsitans**

* Much more important than other species listed

G palpalis—always in vicinity of water pupates close to water in dry shaded places closely associated with man feeds on crocodiles animals man

G tachinoides—pupates in dry sandy soil near water never closely associated with man feeds largely on game

G morsitans—open country pupates in dry friable earth feeds on animals and man

somes observed in the patient's blood in the presence of a heavy infection are derived from these They pass down the salivary ducts entering the bite wound through the channel in the hypopharynx The fly becomes infective in 18 to 34 days after the infecting meal

In the presence of epidemic outbreaks of the disease it is possible that mechanical transmission of the trypanosomes from man to man occurs both by the tsetse flies and possibly the biting fly, *Stomoxys* as the result of interrupted feedings in the course of which the proboscis has become contaminated with trypanosomes

Incidence There is no significant variation in incidence by age sex and occupation except insofar as these factors may contribute to exposure to the flies While there is no true racial immunity it is gen erally considered that the disease tends to be more acute in the white race than in the colored

Pathology. The essential pathologic changes of trypanosomiasis are found in the lymph nodes and in the central nervous system In the early stages there is proliferation of lymphoid tissue In the chroni stages a productive endarteritis occurs with endothelial proliferatio involving especially the small vessels and accompanied by perivascul infiltration with plasma cells and lymphocytes giving many of the lesio a histologic appearance similar to those of syphilis Chronic inflammat of the lymphatic system results in enlargement of the lymph nodes wh in the early stages frequently contain trypanosomes At this stage th is usually some enlargement of the spleen

Central nervous system involvement results essentially in a menin encephalitis and meningomyelitis. These are accompanied by peri cular plasma and round cell infiltration which is most marked in pia arachnoid of the brain and cord particularly about the vesse the pons and medulla (Fig VI 56) The brain and cord are conge hemorrhages may be present and trypanosomes are frequently scat through the brain substance At times small granulomatous lesion encountered especially in the cortex

Prior to involvement of the nervous system the cerebrospinal reveals no abnormalities When lesions are established howeve and is usually under increased pressure and the cell count may

1000 per cubic millimeter There is a positive globulin reaction and the centrifuged fluid frequently reveals trypanosomes

Clinical Characteristics The clinical manifestations of trypanosomiasis may vary greatly in their intensity and duration The bite of the infected tsetse fly is often followed by a local inflammatory reaction of the skin which may last 48 to 72 hours The incubation period of the disease may show great variation in occasional instances lasting apparently two to five years before the appearance of clinical symptoms Its usual duration however is ten days to three weeks

The disease may be divided into two clinical stages The first that of invasion by the trypanosomes is characterized by fever and lymph adenopathy The second stage is marked by the onset of central nervous system involvement and is characterized by the symptoms and signs of a meningo encephalitis and meningomyelitis with cachexia and ultimately in the most severe cases coma and death

In the stage of invasion trypanosomes are present in the peripheral blood but may be more readily demonstrated in fluid aspirated from enlarged lymph nodes (Fig VI 57) The irregularly remitting fever may be high Characteristically the temperature is normal or close to normal in the morning rising to 103° or 104° F at night The pulse and respiration are correspondingly elevated Early in the disease headache neuralgic pains insomnia and loss of ability to concentrate are common In white individuals there is frequently an irregular circinate rash most commonly observed on the trunk and thighs This usually appears as irregular oval pinkish erythematous areas having a clear center Pruritus is common and often severe Painful local edemas of the hands the feet about the eyes and in the vicinity of various joints are frequent and characteristically transitory All these symptoms and signs including the

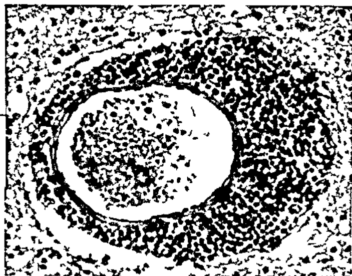


Figure VI.56. African sleeping sickness section of brain showing perivascular infiltration (cuffing) and edema.

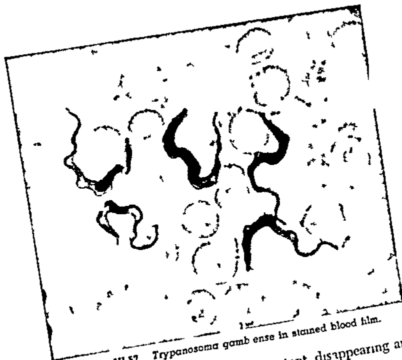


Figure VI 57 *Trypanosoma gambiense* in stained blood film.

febrile reaction may be irregular and inconstant disappearing and reap-
pearing after varying intervals

As the infection becomes established the superficial lymph nodes become enlarged This is most evident in the posterior cervical chain where the swelling constitutes one of the most important diagnosti criteria Winterbottom s sign This is such a constant accompanimen of African trypanosomiasis that examination for enlargement of th posterior cervical nodes is a useful procedure for survey purposes (F VI 58) The individual nodes are discrete varying from 1 0 to 1 5 c diameter At first they are soft and elastic later becoming hard as esult of fibrotic changes The enlargement usually persists from econd to the sixth month of the disease With the involvement he lymphatic system there may be some enlargement of the spleen liver which with the fever may be suggestive of a malarial infection

During this first stage of the disease deep hyperesthesias espec over the ulna (Kerandel s sign) are frequent

Involvement of the central nervous system may occur early i disease In consequence lumbar puncture and careful spinal flu amination are essential

The total leukocyte count is usually normal There is characteri a relative mononucleosis with increased numbers of both large an mononuclear cells which may constitute 50 to 70 per cent of th white blood cells

The second stage that of involvement of the central nervous may occur early in the clinical course of the infection or may velop until months or even years later The onset of this stage i ... It may be ushered in by tremor of the tongue an ... hysteria mania and other signs of mening

alitis and meningomyelitis The common presenting symptom is a gradually increasing languor and lassitude This is followed shortly by the appearance of tremor of the tongue and fingers With further progression the facial expression is altered, the patient appears apathetic, morose and lethargic, somnolence is common Speech is slow and mumbling, the gait becomes shuffling, and fine fibrillary tremors of the tongue and of the muscles of the forearms are prominent

With still further progression the typical sleeping sickness stage is reached The somnolent state is almost continuous, and it becomes increasingly difficult to arouse the patient Ultimately this progresses to true coma Concurrently there is progressive development of marasmus with wasting increasing muscular weakness, increasing tremor and dribbling of saliva Late in the disease epileptiform convulsions may occur Death ensues as the result of sleeping sickness itself, malnutrition, or intercurrent infection (Fig VI 59)

Diagnosis. The diagnosis of trypanosomiasis depends upon the demonstration of the trypanosomes in the peripheral blood, in fluid aspirated from enlarged lymph nodes or in the spinal fluid Frequently trypanosomes are rare or impossible to find in the peripheral blood

Examination of a stained smear of fluid aspirated from an enlarged elastic lymph node is the most dependable diagnostic procedure in the early stages of the disease It is not of value in the later stages when the nodes have become hard and sclerotic A fine hypodermic needle should be introduced into the substance of a lymph node and the aspirate used to prepare thick and thin films These should be stained with Wright's, Giemsa's or Leishman's stains

Examination of the blood should include the study of both thick and



Figure VI.58 Enlargement of posterior cervical lymph nodes—Winterbottom's sign. (Courtesy of Dr James R. Busvine London School of Hygiene and Tropical Medicine)



Figure VI.59 Comatose stage of sleeping sickness (Courtesy of E. R. Kellersberger in Strong Still's Diagnosis Prevention and Treatment of Tropical Diseases The Blakiston Co)

thin smears In fresh unstained cover slip preparations the motility of the trypanosomes may reveal their presence even when few are present The most certain method, however, entails the use of centrifuged citrated blood The technique is described on page 801

The cerebrospinal fluid should be examined in all cases In the stage of early involvement of the central nervous system there may be only a slight increase in the cell count and a positive globulin reaction Even in this stage trypanosomes may be demonstrable after centrifuging th fluid As the involvement becomes more extensive, the cell count rise the pressure is increased and the fluid may have a ground glass appe ance or may even be turbid The cells are predominantly mononuclea Examination of the blood of rats guinea pigs or monkeys after inocu tion with lymph node aspirates, blood or spinal fluid from the pat may reveal trypanosomes when other methods fail

Treatment. *General Measures* Lumbar puncture should be formed immediately, periodically through the course of treatment, ar least twice at intervals of six months after completion of treatme ensure early recognition of central nervous system invasion It i portant to emphasize that the earlier efficient therapy is initiatec greater are the possibilities of cure

The drug treatment of trypanosomiasis presents three aspect early case the intermediate and advanced case in which inva the central nervous system has occurred, and chemoprophylaxis

Early Cases Two drugs are recommended for treatment stage prior to invasion of the central nervous system

Suramin Synonyms Naphuride, Bayer 205, Antrypol I -neau 309, Germanin The drug is a complex organic chemic

contains no heavy metal It combines with the plasma proteins and remains in the circulating blood for long periods It is excreted through the kidneys and frequently acts as a renal irritant causing albuminuria with yellowish granular casts More rarely, administration of the drug may be followed by nephritis and uremia Urinalyses should be performed the day after each treatment and therapy must be discontinued if evidence of renal irritation appears

Suramin is still the drug of choice for the early stages of trypanosomiasis and is considered to be particularly useful in cases of infection by *T rhodesiense* It is ineffective against infection of the central nervous system The drug may be given intramuscularly or intravenously the latter is the preferred route of administration It must not be given intrathecally because of its irritating effects

Suramin is administered intravenously at four day intervals dissolved in 10 ml of distilled water The initial dose should not exceed 0 3 to 0 5 gram because of possible idiosyncrasy Subsequent doses should be 1 0 gram and should be continued until a total of 10 0 grams has been administered The dosage for children is reduced in accordance with age and weight

Pentamidine Synonyms M&B 800 Lomidine The drug is an aromatic diamidine available in two forms

Pentamidine the isethionate 1 74 mgm equivalent to 1 mgm of the base

Lomidine the methanesulfonate 1 56 mgm equivalent to 1 mgm of the base

Although it may be administered by mouth the recommended routes are by intramuscular or intravenous injection When given too rapidly by vein it may cause a sudden fall of blood pressure This depressor effect may be prevented by slow administration with the patient in the recumbent position or by intramuscular injection of 0 25 ml of 1/1000 epinephrine or by an antihistaminic given just before the injection of pentamidine In some instances blood sugar levels are depressed

Pentamidine is quite effective in early cases but is less reliable Solutions of pentamidine must be freshly prepared using sterile distilled water For intramuscular injection the average dose is 4 mgm per kilogram of *body weight dissolved in not more than 3 ml of sterile distilled* water for intravenous administration the dose is 2 to 4 mgm per kilogram of body weight dissolved in 5 to 10 ml of sterile distilled water

The drug may be given daily or on alternate days for a total of 8 to 10 injections When administered concurrently with suramin the depressor effects of pentamidine seem to be reduced

Later Cases The onset of the later stages of the disease is marked by the development of central nervous system symptoms and signs and abnormalities of the cerebrospinal fluid There are two drugs which are

which is reduced in the body to the active trivalent form It is freely soluble in water The margin of safety between the therapeutic and the

toxic dose is small In a susceptible person even a small dose may cause circulatory collapse and a full dose death The common toxic effect however is optic atrophy This may lead to permanent blindness The development of actual optic atrophy is commonly preceded by definite ocular symptoms including photophobia lacrimation ocular pain or dimness of vision

Tryparsamide penetrates through the "blood brain barrier" and kills trypanosomes in the nervous tissue However it is more effective against *T gambiense* than *T rhodesiense* Because of its relative ineffectiveness against the parasites in the blood and lymph pentamidine or suramin are usually given in the intervals between the weekly injections of tryparsamide Incomplete treatment is an important factor in the development of tryparsamide resistant strains

It is preferable to administer the drug intravenously dissolved in 10 ml of sterile distilled water although it may be given intramuscularly Salt solution *must not* be used Individual doses should be 0 04 to 0 05 gram per kilogram of body weight Children up to 12 years of age seem to tolerate this drug and may be given up to 0 08 gram per kilogram of body weight The initial adult dose should be 1 0 to 1 5 grams and subsequent doses 2 0 to 3 0 grams depending upon the weight of the patient Fifteen weekly injections should be given

Mel B The drug is a compound of Melarsen oxide with BAL containing trivalent arsenic Mel B should be given only under close supervision in hospitals and not in field dispensaries because of its toxicit However if the dosage is carefully regulated and attention is paid to th condition of the patient toxicity should not be a serious problem It h given good results in advanced cases and in infections which are fractory to other forms of treatment Mel B is regarded by some as be superior to tryparsamide for advanced cases

The recommended dosage is 3 6 mgm per kilogram of body wei given intravenously on each of four consecutive days After a rest pe of one week the course is repeated While Mel B may be regarde still on trial especially in the treatment of early cases the combin of Suramin and Mel B appears promising

OTHER DRUGS A number of other drugs are being given cl als Some of these seem to hold considerable promise For exa sobal is valuable in the treatment of resistant strains of huma nosomes but its toxicity is high and hence great care must be sed in its use Puromycin (Stylomycin) is therapeutically active a *gambiense* in man

Prophylaxis The recognition isolation and effective ther nfected persons constitutes one of the most important measure prophylaxis of trypanosomiasis Individuals entering disease fre from regions in which the disease is endemic should invariabl amined and subjected to medical control and treatment if infect is particularly true of native populations imported for labor pu

The second important control measure is directed against th In fly infested areas individuals should wear suitable clothing l eyes and long trousers The flies are attracted by movi

and will frequently follow individuals or automobiles for considerable distances They bite easily through thin clothing. Motor vehicles passing into a controlled area should be carefully examined for the presence of the tsetse Insofar as possible heavily infested areas should be avoided It has been necessary on occasion in the past to evacuate population groups of considerable size from regions where satisfactory control of *Glossina* was not practicable

Two drugs have proved to be effective chemoprophylactic agents *Naphuride* and *pentamidine* Suramin in dosage of 1 0 gram every two to three months exercises a definite protective action However pentamidine has been shown to confer a high degree of protection over a longer period.

Mass chemoprophylaxis using pentamidine has been greatly extended and has given highly encouraging results In areas where injection has been repeated four to five times at intervals of six months the new infection rate has been reduced by 90 to 95 per cent It appears that mass treatment may prove to be a most important factor in the control of trypanosomiasis Pentamidine does not cause abortion

Dosage Naphuride 1 0 gram every two to three months Pentamidine 3 mgm per kilogram of body weight every six months

44

American Trypanosomiasis

Chagas Disease

Victor M Arean

Synonyms South American trypanosomiasis schizotrypanosomiasis opilacao enfermedad de Chagas

Definition This is a relatively uncommon acute and chronic disease produced by infection with *Trypanosoma cruzi* that especially affects children and young adults It is characterized pathologically by the presence of trypanosomes in the blood and leishmanias in the tissues The acute stage is manifested by fever facial and general edema adenitis anemia and the presence of subcutaneous nodules (panniculitis) The symptoms in the chronic stage depend upon the localization of the parasite in the heart the central and autonomic nervous systems liver spleen and other organs

Distribution. The disease is limited primarily to rural areas of Brazil Uruguay Argentina Chile Mexico and other South and Central

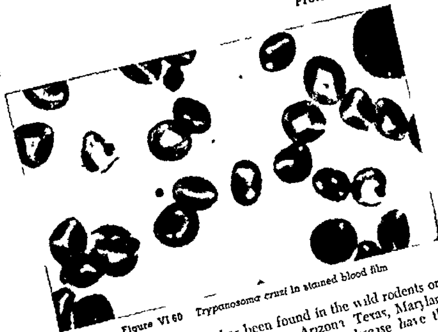


Figure VI 60 *Trypanosoma cruzi* in stained blood film

American countries, *T cruzi* has been found in the wild rodents or othe animal hosts in California, New Mexico, Arizona Texas, Maryland an Louisiana Two authenticated cases of Chagas' disease have thus f been diagnosed in the United States

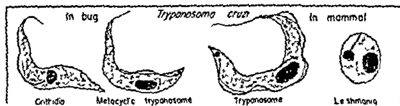
Etiology. *Trypanosoma cruzi* is a pleomorphic trypanosome havi two phases in its life cycle One occurs in man and other mammals, a one in the transmitting insects In the infected mammal typical trypa somes are present in the blood, leishmanias and transformation sta occur in the endothelial and tissue cells

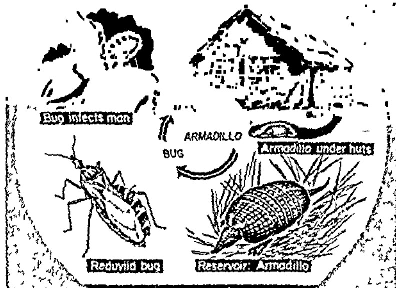
The trypanosome is approximately 20 μ in length, often spindle sha and presents both long and short forms The nucleus is centrally pla and the characteristically large oval kinetoplast is situated posteri An axoneme arises from the dotlike kinetoplast complex and is exte along the margin of a narrow undulating membrane It presents folds, becoming a free flagellum anteriorly Characteristically this anosome presents a sharp wedge shaped posterior extremity In st films the parasites usually appear C or U shaped Dividing fon not occur in the blood (Fig VI 60)

The trypanosomes invade tissue cells, lose the flagellum and lating membrane and assume the leishmanial form, these are ro oval bodies 3 to 5 μ in diameter, presenting both a nucleus and a plast *Trypanosoma cruzi* may be grown on artificial culture me p 823)

Epidemiology. The reservoirs of *T cruzi* are man and oth mals, especially the armadillo and opossum Dogs cats, bats, mestic pig the house rat and various other mammals, including two species of monkeys, have been found naturally infected

The infection is transmitted from man to man and from a animal to man by the reduviid (cone nose) bugs also known or kissing bugs The latter designation is based on the fact tha ...cious biters and attack the face especially





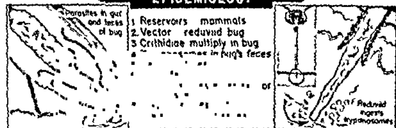


Figure VI.61 Epidemiology of Chagas disease

The reduviid becomes infective eight to ten days after ingestion of *T. cruzi* and may remain infective for as long as two years. The reduviids particularly concerned in the transmission of Chagas' disease are *Panstrongylus megistus* and *P. infestans*. Other species of the genus are also vectors. The infection may likewise be transmitted by allied genera, such as *Rhodnius*, *Eratyrus* and *Eutriatoma*.

The reduviid bugs frequently inhabit the burrows of armadillos and likewise adapt themselves to living in poorly constructed rural houses They are also commonly found in outbuildings such as stables and pig sties During the day they remain in cracks and holes or in thatch com ing out at night to feed They tend to remain in the same house as long as it is inhabited (Fig VI 61)

After ingestion by the bug the trypanosomes multiply in the midgut by longitudinal fission with the development of noninfective crithidia which have a centrally placed nucleus and a kinetoplast toward the ante rior end Subsequently intermediate forms with a kinetoplast variously situated and metacyclic trypanosomes with the kinetoplast at the poste rior extremity are formed The latter have a well developed undulating membrane and flagellum The metacyclic trypanosomes are found in the hindgut of the reduviid and are passed in its feces When the insect feeds the feces containing metacyclic trypanosomes contaminate the bite wound or an abrasion of the skin or the organisms may penetrate di rectly through the mucous membranes of the conjunctiva or mouth

There is no racial or sex distribution of the infection in man The dis ease is observed at any age although it predominates in children The prognosis is less favorable in those under two years of age

Pathology The parasites multiply rapidly at the site of inoculation where a severe inflammatory reaction is induced this is characterized by the presence of neutrophilic leukocytes round cells marked inter stitial edema and focal lymphangitis (chagoma) The parasites also in vade the fat cells of the affected area where they multiply within th cytoplasm until the host cell disintegrates and a lipogranuloma develop

During the stage of dissemination the parasites can be found in th blood and in any organ or tissue of the body However they show preference for cells of mesenchymal origin (cardiac and skeletal musc reticuloendothelial cells neuroglia)

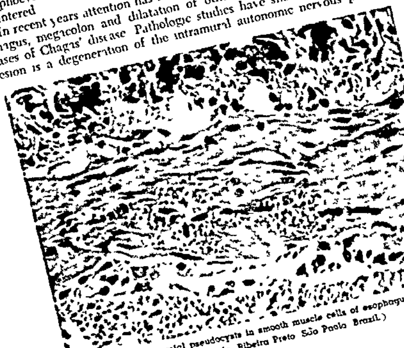
In the infected cells the parasite multiplies by binary fission until la numbers of leishmania fill the cytoplasm and distend the cellular m brane producing a leishmanial pseudocyst (Fig VI 62) Some l mania become elongated produce a flagellum and are transformed crithidial forms These in turn undergo binary fission giving rise to anosome forms which may enter the circulation In humans there multiplication of the trypanosomes in the blood stream The leishm which are released into the interstitial spaces by rupture of the pseu must enter a new host cell promptly otherwise they quickly los capacity to transform into metacyclic forms and soon die As long parasites are intracellular the inflammatory response is minimal sent With disruption of the cell and death of the leishmania to ducts are liberated which immediately induce an inflammatory the severity of which is conditioned by the immunologic state of

In early infections the exudate is composed mainly of neutroph cytes followed later by the appearance of plasma cells lympho histiocytes In older infections the immune state results in the p of granulomatous inflammatory responses of more localized with formation of pseudotubercles and presence of giant cells

...nonparasitized cells may show waxy or hyaline degeneration with
...ual or complete disappearance of cross striations and necrobiosis
...cause the parasite involves cells at random, the inflammatory reaction
...at first focal in nature, however, in massive infections or in chronic
...rocesses, it adopts a more diffuse character. Healing takes place by
...brosis and results in more or less severe degrees of myocardial insuffi-
...iency, depending on the extensiveness of the inflammation. Involvement
of the conduction system of the heart may occur by parasitization of its
fibers or secondary to adjacent fibrosis. Similar changes are also detected
in skeletal muscle and in subcutaneous fatty tissue. In the spleen, liver,
lymph nodes and lungs, there are numerous nodules of hyperplastic
reticuloendothelial cells and histiocytic granulomas. The leishmanias can
be readily observed in the infected muscle fibers, but are more difficult
to see in the reticuloendothelial system or in fat cells.

Meningo encephalitis is an especially severe complication of acute
Chagas' disease, fatalities being highest in small children. In the central
nervous system the inflammatory reaction is characterized by invasion
of neuroglia cells, (Fig. VI 63) the presence of numerous glial nodules
scattered throughout the white and gray substance, basal ganglia and,
more rarely, the cerebellum. Degeneration of neurons, perivascular
lymphocytic cuffing, focal endarteritis and leptomeningitis are also en-
countered.

In recent years attention has been drawn to the frequency of megaeso-
phagus, megacolon and dilatation of other tubular organs in chronic
cases of Chagas' disease. Pathologic studies have shown that the basic
lesion is a degeneration of the intramural autonomic nervous plexuses



VI 62. Leishmanioid pseudocysts in smooth muscle cells of esophagu... (... Dr. Fritz Köberle, Ribeirão Preto, São Paulo, Brazil.)

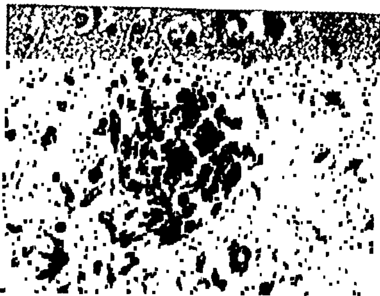


Figure VI.63 Nodules in brain necrosis, cellular proliferation and infiltration.

secondary to the toxic action of *T cruzi* In some instances intramural neurons may be detected, although severe degenerative changes can be recognized in the cytoplasm or nucleus of the affected ganglion cells Extensive experimental studies have given support to the role played by *T cruzi* in the genesis of megaesophagus, megacolon and pathologic dilatation of other tubular organs

Clinical Characteristics. The clinical manifestations of Chagas disease vary markedly In general, the younger the individual the greater the severity of the infection

Acute Chagas' disease is observed mainly in children under two years of age After an incubation period of seven to 14 days high continuous fever, which may reach 104° F, anorexia, vomiting, diarrhea and other systemic symptoms develop, indicating a severe infectious process Frequently there is unilateral conjunctivitis and edema of the eyelids and face, followed by swelling of the lacrimal glands and of the submaxillary lymph nodes (oculoglandular complex, Romaña's sign (Fig VI 64)) In severe cases the edema, nonpitting in character, may spread to other parts of the body There is generalized enlargement of the lymph nodes, *hepatosplenomegaly and meningo encephalic irritation Cardiac arrhythmias*, myocardial insufficiency and collapse are often present and may result in death, in others, the fatal outcome follows extensive damage to the central nervous system

Some children develop a milder type of disease characterized by the presence of numerous subcutaneous painful nodules throughout the body (lipochagomas) There appears to be a peculiar predilection for the involvement of the adipose pad of the cheek (Bichat's pad), because of the extreme tenderness during contraction of the masseteric muscles, the child, after swallowing a few times, refuses to feed and malnutrition

develops In these cases the temperature rises only slightly, but vomiting, diarrhea and signs of tracheobronchitis may be severe and will complicate the picture

The acute stage may resolve completely in a few weeks or months, or may pass into the subacute or the chronic stage Parasitemia, which is found consistently during the febrile periods, may also be observed in individuals who no longer show clinical symptoms of the disease The subacute form is characterized by severe asthenia, mild fever, generalized lymphadenopathy and other symptoms, it may last for months or years In the chronic stage the clinical manifestations are chiefly secondary to myocardial involvement In mild cases the cardiac changes may be limited to tachycardia or extrasystoles, other patients show cardiac arrhythmias, atrioventricular or right bundle branch block In more severe cases there is dilatation of the heart, progressive myocardial insufficiency and eventually cardiac failure, in these patients the electrocardiogram shows widening and notching of the QRS complex and abnormalities in the P and T waves In addition there is generalized lymphadenopathy, mild fever, anemia and occasionally splenomegaly

A common complication of Chagas disease is dilatation of tubular organs In a recent study, 85 9 per cent of 85 cases with megaesophagus gave a positive complement fixation test for Chagas' disease Megaesophagus and megacolon (Fig VI 65) are frequently observed in endemic areas of trypanosomiasis The role played by *T cruzi* in the genesis of these changes has only recently been established

On the other hand the high incidence of hypothyroidism in the same areas, which was once regarded as secondary to chagasic infections, has



Figure VI.64 Ophthalmo-ganglionar complex (Romaña's sign) in Chagas disease (Courtesy of Dr Ramon S. Freire Choco, Argentina.)



Figure VI 85 Megacolon in chronic Chagas disease (Courtesy of Dr Fritz Koberl Ribeira Preto Sao Paolo, Brazil Published in J Trop Med 61 1958)

now been shown to be the result of entirely unrelated causes Neverth
less authenticated cases of chagasic thyroiditis are on record

Diagnosis The diagnosis of Chagas disease is based upon iden
fication of the parasite in blood or tissue samples or by serologic p
cedures Parasitemia may be demonstrated by the following methods

1 Examination of fresh blood films
2 Examination of stained thick and thin blood films
3 Examination of stained films after centrifuging 5 to 10 ml o
trated blood
4 Animal inoculations using 5 to 10 ml of the patient's blood
laboratory animals are easily infected the white rat is a suitable
animal
5 Culture of blood on N N N medium or culture in blood broth
6 Xenodiagnosis Clean uninfected laboratory bred reduviid bu
allowed to feed on the suspected patient Two weeks later the co
of the hindgut are examined for the presence of crithidia and parti
metacyclic trypanosomes In conducting this test it is essential
clean insects properly protected since they can become infec
coprophagy

It is necessary to keep in mind that xenodiagnosis gives a
percentage of positivity and that not all triatomids fed on disea
sons become infected The test gives a higher percentage of
results when repeated several times

Positive parasitemia is to be expected only when blood is
during the acute febrile stage of the disease or during one of th
des of the chronic form When hematologic examinations

tive an alternate procedure is that of obtaining a biopsy from skeletal muscle for the identification of leishmanial forms in muscle cells Biopsy of enlarged lymph nodes (mainly those of the retroauricular or sub

countered in the cephalospinal fluid and then only in cases showing

are occasionally obtained in cases of mucocutaneous leishmaniasis however the clinical picture and signs of this disease are so strikingly different from those of Chagas disease that such cross reactions do not detract from the validity of this test

Treatment. The treatment of Chagas disease is unsatisfactory None of the drugs effective against the African trypanosomes affects *T cruzi* Bayer 7602 and Eagle's 704 are the only available drugs While they appear to be useful in controlling acute symptoms in young children they do not free the blood of trypanosomes There is no preparation which is effective against the leishmanial forms in the tissues In consequence treatment is largely symptomatic

Prophylaxis Native houses and adobe and thatched huts in the endemic area should not be used for sleeping quarters since they constitute the normal harborage of the insect vector Some protection of individuals resident in such structures may be afforded by proper use of bed nets since the vectors are nocturnal feeders

Reports concerning the value of residual spraying with DDT are conflicting However Gammexane is highly effective in controlling the reduviid bug population when used as a residual spray inside buildings and huts It is claimed that entire reduviid bug populations have been eliminated by the use of this chemical

routinely and persons having a positive reaction should be eliminated as potential donors

Trypanosoma Rangeli

Human infections with *T rangeli* (Tejera) (probable synonyms *T ariari* and *T guatemalensis*) have been reported from Venezuela Guatemala and Colombia Evidences of pathogenicity or symptoms have not

been observed in persons with natural infections or in human volunteers Natural infections with *T rangeli* have been found in dogs and monkeys and infection with the organism can be induced in laboratory animals Mixed infections of *T rangeli* and *T cruzi* are often encountered Knowledge of the development of *T rangeli* in mammalian hosts is incomplete Dividing forms have been found in peripheral blood and the organism may be isolated from the blood stream several months after infection No intracellular forms have been observed

The trypanosomal forms in peripheral blood are about 30 μ in length The nucleus is anterior to the middle of the organism A small deeply staining parabasal body is present Leptomonad crithidial and metacyclic trypanosomes have been found in the reduviid bug *Rhodnius prolixus* which is the only known vector and in which the organism was first observed It is probable that transmission to man and animals is by the bite of the bug rather than from its excreta

VII

Helminthic Diseases

45

Introduction

Parasitic worms infect man in almost all regions of the world but there is a particular abundance of them in the tropics—an abundance both of species and individuals. This is the result of important climatic and sociologic factors. Many of these parasites require special conditions of temperature and humidity for survival and multiplication. Many others require particular vertebrate or invertebrate hosts such as fish, snails, crustacea or insects for the completion of their life cycles. These hosts in turn gain ready access to man in tropical regions owing to the lack of preventive measures by the indigenous populations. Insect vectors such as various mosquitoes, midges and biting flies are particularly important among these intermediate hosts.

The distribution of those helminthic parasites whose eggs are passed in human dejecta is affected not only by the climatic conditions of rainfall, temperature and humidity but likewise by the sanitary practices of the human population. The almost universal custom in many regions of the world of using human excreta (nightsoil) for fertilizer results frequently in widespread pollution of soil, water supplies and certain foods by which infection is transmitted.

Moreover, racial food habits often determine the incidence of certain of these parasites in man. The practice of eating raw or partially cooked

weak concentrations of vinegar or brine are an important potential source

fection since eggs of *Ascaris* and *Trichuris* have been shown to re
viable in such foods for considerable periods

The parasitic helminths of man fall into two main groups the round
worms or Nemathelminthes and the flatworms or Platyhelminthes The
former are characterized by their unsegmented undifferentiated external
appearance (except the spiny headed worms) slender shape and their
mouth or occasionally striated cuticula The Nemathelminthes consist of
three groups only one of which the threadworms roundworms (*sensu
stricto*) or Nematoda contains important human parasites

The flatworms or Platyhelminthes are flattened dorsoventrally and
sometimes exhibit pseudosegmentation The flatworms parasitizing man
include the leaflike flukes or Trematoda and the ribbon like pseudo
segmented tapeworms or Cestoda

One other group the spiny headed worms or Acanthocephala should
be mentioned briefly These are often placed in the same phylum as
roundworms or Nemathelminthes The sexes are separate and both males
and females have a retractile proboscis armed with spines and a cylindri
cal body which lacks a digestive tract but contains other organ systems
Only two species of Acanthocephala parasitize man and infections by
these are rare Therefore they will not be considered further in this book

The parasitic way of life has brought about numerous modifications in
structure function and even life cycles Some of these changes are char
acteristic of groups while others may be peculiar to given genera or
species For example the integument or cuticula of helminths secreted
by the underlying cells forms a hardened tough and elastic or delicate
covering which is resistant to digestion during the life of the parasite
Often it is specialized to form hooks or cutting plates such as occur in
the buccal cavity of hookworms the stylets of the microfilariae or other
spines spicules or hooks Both the trematodes and tapeworms may pos
sess circular suckers or acetabula that serve as holdfast or locomoto
organs However in some species of tapeworm such as *Diphyllobothriu
latum* the holdfast device is a poorly developed although very efficie
pair of sucking grooves Many helminths possess glands which open n
the mouth and these are believed to secrete an enzyme like substa
which causes tissue destruction Some parasites use this tissue dire
as food whereas for others the destruction merely makes it possibl
them to penetrate to a definitive location within the host

Many organs of locomotion nutrition and reproduction have u
gone marked changes in parasitic organisms Parasites usually are
ported from place to place by the host and in many instances th
be transmitted passively from one host to another This has been
ated with a reduction in the development of locomotor devices
of nutrition have become modified or even lost as in the ca
tapeworms On the other hand the reproductive organs have u
considerable development and are often larger and more co
than those found in free living relatives Frequently the pro
tremendous quantities of eggs is associated with the slender
g or larva will succeed in reaching and establishing
host These structural or physiologic differe

characteristics of the large groups or perhaps only of genera or species

Helminths almost without exception do not multiply in man as adults thus differing signally from other disease producing organisms The pathologic changes which they induce in the host are the effects of a variety of mechanisms Thus the hookworm is a voracious feeder upon blood which it obtains through lacerations of the intestinal mucosa produced by its cutting plates or teeth Certain of the tapeworms merely rob the host of food whereas others utilizing man as an intermediate host for their larval forms produce single or multiple expanding tumors in many anatomic locations Other parasites entering the skin cause more or less severe dermatitis probably the result of toxic secretions enzymes or metabolites of the larvae after penetration Certain helminths produce pathologic changes in the subcutaneous tissues the eye the l other viscera in the course of the migrat ns f Certain of the filarial system cause acute an l lymphatic obstruction the smaller venous channels of the bowel and vesical walls produce eggs of the schistosomes deposited in s be followed by vascular damage and ulceration into the viscus Further the mechanical irritation from the eggs or chemical irritation from products of the contained embryo appears to induce epithelial hyperplasia and metaplasia which may be followed occasionally by carcinoma

Thus the pathologic changes accompanying helminthic infections may be both varied and severe and the resulting clinical phenomena those of serious and acute or chronic disease It has been estimated that over two and a quarter billion helminthic infections are harbored by the world population More that 800 million humans are infected with one or more species of worms The diseases caused by parasitic worms constitute a most important segment of tropical medicine The practicing physician must be familiar with this group of conditions their epidemiology pathology clinical manifestations and the life cycles of the parasites if he is to practice either therapeutic or preventive medicine successfully

Endemic areas of worm infections certainly are not limited to the tropics and subtropics Infections are frequently observed in temperate areas in migrant population groups or in travellers who acquired their infections in the tropics Thus physicians outside the tropics also must have adequate knowledge of helminthiases

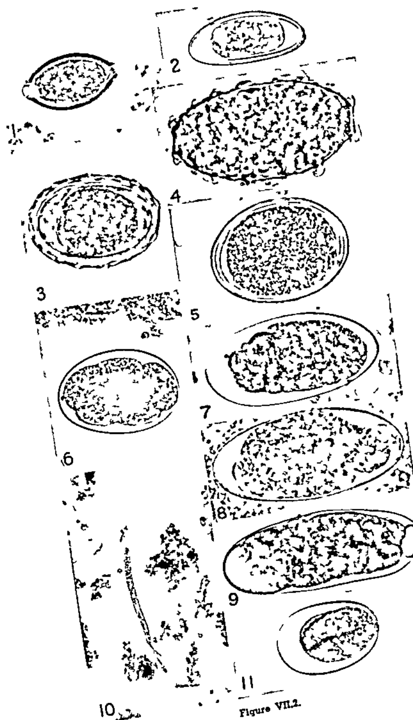


Figure VII.2.

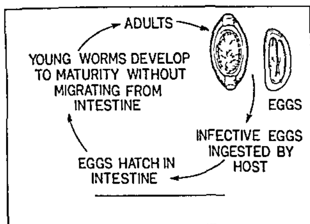


Figure VII.3 Nematode cycle—direct type

Nematode Eggs The eggs contain the fertilized cell and yolk granules which are surrounded by a vitelline membrane in a chitinous shell (Fig VII 2) Sometimes this in turn has an outer protein covering as in *Ascaris* eggs Unsegmented partially developed or embryonated eggs may be discharged or the larvae may be already hatched Unsegmented eggs are typical of *Ascaris* and whipworm whereas the eggs of hookworms usually show signs of development Pinworm eggs are embryonated when passed whereas in the case of some microfilariae *(W bancrofti)* the original shell is stretched to form the sheath Larvae or nonsheathed microfilariae are liberated by such parasites as *Trichinella spiralis* and *Onchocerca volvulus* respectively

The Generalized Cycle of the Intestinal Nematodes

The life cycles of the intestinal nematodes fall into one of several categories on the basis of developmental sequences (1) direct (2) modified direct and (3) skin penetrating types

The Direct Type No intermediate host is required the adult worms develop directly from eggs reaching the alimentary canal of man Whipworm *Trichuris trichiura* and pinworm *Enterobius vermicularis* are examples of this type Whipworm eggs passed in the stool require a

---

Figure VII.2. Some common nematode eggs (1) whipworm, *Trichuris trichiura*, (2) pinworm, *Enterobius vermicularis* (3) large roundworm, *Ascaris lumbricoides* fertilized egg (4) *Ascaris* unfertilized egg (5) *Ascaris* decorticated egg (6) hookworm egg (7) immature egg of *Trichostrongylus orientalis* (8) embryonated egg of *T orientalis* (9) egg of *Meloidogne javanica* a plant nematode which sometimes is found in stools (10) rhabditiform larva of *Strongyloides stercoralis* the stage usually found in the stool (11) egg of *S. stercoralis* rarely seen in the stool. All figures 500 × except (10) 75 × (Nos. 5 and 6 courtesy of the Photographic Laboratory AMSGS photos by Milt Cheskis. Nos 7 8 and 9 courtesy of Dr T B Magath. Mayo Clinic. All others courtesy of Dr R. L. Roudabush, Ward's Natural Science Establishment. Rochester N Y photos by T Romaniak)

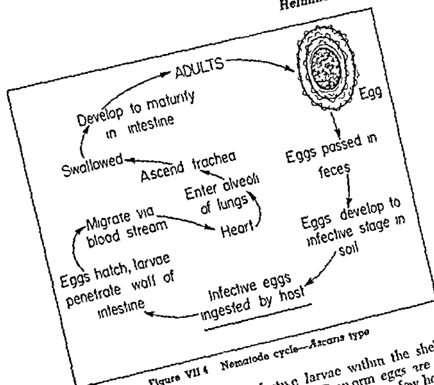


Figure VII 4 Nematode cycle—*Ascaris* type

period for the development of infective larvae within the shell, after which time they become infective for man Pinworm eggs are embryonated when deposited and become infective for man in a few hours after deposition (Fig VII.3)

The Modified Direct Type. *Ascaris* eggs are unsegmented when passed in the feces and require a period for embryonation before becoming infective for man Ingested embryonated eggs hatch in the intestine of man and the larvae penetrate the intestinal wall to reach the cir culatory system Surviving larvae leave the capillary beds of the lung and migrate up the respiratory tract to the esophagus and thence down through the stomach to the intestine, where they mature (Fig VII 4)

The Skin Penetrating Type. Members of this group pass partiall developed eggs or rhabditiform larvae in the stool The former eventu ally hatch into noninfective rhabditiform larvae Such larvae continue grow molt several times, and become transformed into infective or fila form larvae capable of penetrating the exposed skin surface of man I veloping eggs are found in the stools of persons infected with hookwor but larvae are characteristically present in the feces of those infec with *Strongyloides stercoralis*

In both hookworm disease and strongyloidiasis, the filariform la which penetrate the skin of man reach the circulatory system and eve ally the capillary beds of the lungs There they leave the capillaries, to the alveoli and migrate up the respiratory tract and down the esc gus to the intestine, where maturation takes place (Fig VII 5) *Strongyloides stercoralis* differs from hookworm in several impo respects Under some conditions the rhabditiform larvae may tran ling adult males and females which reproduce in the s

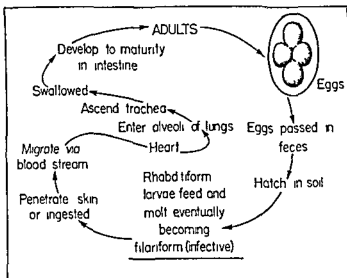


Figure VII.5 Nematode cycle—hookworm type

other cases filariform larvae develop in the intestinal or rectal area These directly penetrate the bowel or the perianal skin with resultant autoinfection

Trichuriasis

Synonyms Trichocephaliasis whipworm infection

Definition Trichuriasis is an infection of the human intestinal tract caused by the nematode *Trichuris trichiura*

Distribution. *Whipworm is a cosmopolitan parasite but is most* abundant in the warm moist regions of the world In various areas studied it has been found in 1 to almost 100 per cent of the population The calculated number of whipworm infections in man throughout the world is 355 million

Etiology MORPHOLOGY Adult whipworms *Trichuris trichiura* (Linnaeus 1771) Stiles 1901 [= *Trichocephalus trichiurus* (Linnaeus 1771) Blanchard 1895] usually are partially imbedded in the mucosa of the large intestine The parasites have a characteristic whiplike shape The anterior portion is long and threadlike the posterior portion is broader and comprises about two fifths of the worm The female parasites *range between 35 and 50 mm long the males are slightly smaller* measuring 30 to 45 mm Anteriorly the mouth opens into a delicate esoph

agus, characterized by a narrow lumen surrounded by a single row of cells, which extends through most of the narrow anterior three fifths of the body. The male reproductive organs open into a posterior cloaca. The caudal region of the male is often coiled. There is a retractile penial sheath with a bulbous spined tip through which protrudes the single copulatory spicule. The female reproductive system also consists of a single set of reproductive organs, the external pore of which opens at the anterior extremity of the thickened body proper.

The barrel-shaped eggs when passed in the stool are undeveloped, ranging between 50 and 54 μ by about 22 μ, and are provided with a characteristic clear knob or mucoid plug at either end. The eggs have a double shell, the outer portion of which is usually bile-stained. A female whipworm produces between 3000 and 7000 eggs per day (Fig. VII 2).

Development. The unsegmented eggs require a minimum of ten days under optimal conditions of moisture and temperature for development in soil. Under less favorable circumstances embryonation may require several months.

After ingestion the infective eggs hatch in the upper duodenum and the larvae become attached to the villi of the intestine where they remain and grow for about a month. At maturity the adult parasites leave their primary site of attachment and pass down the intestine to their final habitat in the cecum and proximal colon. In heavy infections they may also localize in the terminal ileum, appendix and much of the large intestine (Fig. VII 3).

Epidemiology. The distribution of whipworm is largely coextensive with that of *Ascaris*, and the epidemiology of the two species is somewhat similar (see p. 410). The former, however, predominates in areas of heavy rainfall, high humidity, dense shade and moist soil. *Ascaris* on the other hand, is more prevalent in regions of lesser rainfall and shade. The eggs of *Trichuris trichiura* do not withstand exposure to direct sunlight and are destroyed by drying. They are unlikely to develop to the infective stage on cinders, ashes or hardened clay (Fig. VII 14).

Pathology. The anterior portions of the parasites are interlaced through the mucosa of the cecum and appendix. In heavy infections, the nematodes may be found throughout the colon and in the rectum. Ordinarily there is no marked tissue reaction, although liquefaction of the cells and bleeding in proximity to the parasites may occur. Secondary bacterial infection may cause inflammatory lesions (Figs. VII 6, VII 7).

Severe infections may be accompanied by a moderate eosinophilia and ... numerous Char

... nfections usually ... urden may be as- ... ration, dysentery, mucoid stools, abdominal pain and tenderness, dehydration, severe anemia, weight loss and weakness. Occasionally prolapse of the rectum occurs. Adult worms may be observed on the prolapsed bowel or by sigmoidoscopy. Some patients with heavy infections are acutely ill.

Diagnosis. Diagnosis depends upon the recovery from the feces of the characteristic double shelled, bile stained eggs with mucoid plugs These may be detected in direct smears, by formalin ether (MGL or AMS III) centrifugal sedimentation methods, or by flotation techniques (see pp 809–
rect fecal sme
smear in pat
probably is coincidental, and other causes of the patient's symptoms should be sought

Treatment. Dithiazanine iodide (Delvex, Telmid, Dilombrin, Netocyd) is an effective oral therapeutic for trichuriasis The dosage for adults on the first day is 100 mgm three times daily two hours after meals On the second and subsequent days, the dosage is increased to 200 mgm three times daily The dosage is reduced proportionately for children Treatment is given from five to 15 days, depending on the size and severity of the infection Untoward reactions which may be encountered at times include nausea, vomiting, abdominal cramping and diarrhea

An alternate, though less practical method of treating patients with clinical trichuriasis is the use of hexylresorcinol enemas Prior to treatment the bowel is cleansed with saline enemas, and the buttocks, thighs and other areas likely to be exposed to the expelled enemata are coated liberally with petroleum jelly to protect the skin A 22 caliber rubber



Figure VII.6



Figure VII.7

Figure VII 6. Masses of *Trichuris trichiura* (whipworms) in colon of a child (Courtesy of The Louisiana State University School of Medicine)

Figure VII.7. Section of large intestine showing adult whipworms (natural infection of *T vulpis* in dog) Thin anterior portions of worms are imbedded and threaded in the mucosa broader posterior parts of worms containing eggs are in lumen. (Courtesy of The Louisiana State University School of Medicine)

agus characterized by a narrow lumen surrounded by a single row of cells which extends through most of the narrow anterior three fifths of the body The male reproductive organs open into a posterior cloaca. The caudal region of the male is often coiled There is a retractile penial sheath with a bulbous spined tip through which protrudes the single copulatory spicule The female reproductive system also consists of a single set of reproductive organs the external pore of which opens at the anterior extremity of the thickened body proper

The barrel shaped eggs when passed in the stool are undeveloped ranging between 50 and 54 μ by about 22 μ and are provided with a characteristic clear knob or mucoid plug at either end The eggs have a double shell the outer portion of which is usually bile stained A female whipworm produces between 3000 and 7000 eggs per day (Fig VII 2)

Development The unsegmented eggs require a minimum of ten days under optimal conditions of moisture and temperature for development in soil Under less favorable circumstances embryonation may require several months

After ingestion the infective eggs hatch in the upper duodenum and the larvae become attached to the villi of the intestine where they remain and grow for about a month At maturity the adult parasites leave their primary site of attachment and pass down the intestine to their final habitat in the cecum and proximal colon In heavy infections they may also localize in the terminal ileum appendix and much of the large intestine (Fig VII 3)

Epidemiology The distribution of whipworm is largely coextensive with that of *Ascaris* and the epidemiology of the two species is somewhat similar (see p 410) The former however predominates in areas of heavy rainfall high humidity dense shade and moist soil *Ascaris* on the other hand is more prevalent in regions of lesser rainfall and shade The eggs of *Trichuris trichiura* do not withstand exposure to direct sunlight and are destroyed by drying They are unlikely to develop to the infective stage on cinders ashes or hardened clay (Fig VII 14)

Pathology The anterior portions of the parasites are interlaced through the mucosa of the cecum and appendix In heavy infections the nematodes may be found throughout the colon and in the rectum Ordinarily there is no marked tissue reaction although liquefaction of the cells and bleeding in proximity to the parasites may occur Secondary bacterial infection may cause inflammatory lesions (Figs VII 6 VII 7)

Severe infections may be accompanied by a moderate eosinophilia and by anemia The dysenteric exudate sometimes contains numerous Charcot Leyden crystals and eosinophils

Clinical Characteristics Very light whipworm infections usually produce no symptoms The presence of a large worm burden may be associated especially in children with diarrhea of long duration dysentery mucoid stools abdominal pain and tenderness dehydration severe anemia weight loss and weakness Occasionally prolapse of the rectum occurs Adult worms may be observed on the prolapsed bowel or by sigmoidoscopy Some patients with heavy infections are acutely ill

Diagnosis Diagnosis depends upon the recovery from the feces of the characteristic double shelled, bile stained eggs with mucoid plugs These may be detected in direct smears, by formalin ether (MGL or AMS III) centrifugal sedimentation methods, or by flotation techniques (see pp 809–811) In clinical infections eggs usually are numerous in direct fecal smears When only a few whipworm eggs are found in a direct smear in patients with diarrhea or dysentery, the helminthic infection probably is coincidental, and other causes of the patient's symptoms should be sought

Treatment. Dithiazanine iodide (Delvex, Telmid, Dilombrin, Netocyd) is an effective oral therapeutic for trichuriasis The dosage for adults on the first day is 100 mgm three times daily two hours after meals On the second and subsequent days, the dosage is increased to 200 mgm three times daily The dosage is reduced proportionately for children Treatment is given from five to 15 days, depending on the size and severity of the infection Untoward reactions which may be encountered at times include nausea, vomiting, abdominal cramping and diarrhea

An alternate, though less practical method of treating patients with clinical trichuriasis is the use of hexylresorcinol enemas Prior to treat



Figure VII 6



Figure VII 7

Figure VII.6. Masses of *Trichuris trichiura* (whipworms) in colon of a child (Courtesy of The Louisiana State University School of Medicine)

Figure VII.7. Section of large intestine showing adult whipworms (natural infection of *T vulpis* in dog) Thin anterior portions of worms are imbedded and threaded in the mucosa broader posterior parts of worms containing eggs are in lumen. (Courtesy of The Louisiana State University School of Medicine)

catheter is introduced through the anus about 15 cm From 400 to 500 ml of a 0 2 per
Retention may
ing the free end
hexylresorcinol suspension should be expelled after retention for one-half hour If necessary, a small saline enema may be used to initiate expulsion Retention enemas may be repeated at four day intervals for a total of three or four times, *if necessary*, as indicated by the consistency of the stools

Treatment for Mixed or Multiple Helminthiases Since ascarids and whipworms frequently coexist in the same host, dithiazanine iodide is a suitable therapeutic for mixed infections with these two helminths (see pp 403, 414) This drug is a broad spectrum anthelmintic that is effective against ascariasis, trichuriasis, strongyloidiasis and enterobiasis and has moderate activity against hookworm In addition to being the drug of choice for the treatment of trichuriasis and strongyloidiasis dithiazanine iodide is of value in treating persons with mixed or multiple intestinal nematode infections which occur so commonly in tropical and subtropical areas

Prophylaxis. Prophylaxis depends upon sanitary disposal of human feces, washing of the hands before eating, avoiding raw vegetables in areas where human excreta are used for fertilizer and supervision of children to prevent dooryard defecation and coprophagy

Enterobiasis

Synonyms. Oxyuriasis, pinworm or seatworm infection

Definition. Enterobiasis is an infection of the human intestinal tract by the pinworm, *Enterobius vermicularis*

Distribution. Enterobiasis is a cosmopolitan infection Surveys in various parts of the world indicate that *E vermicularis* is probably the most widely distributed human helminth, its incidence varying from 1 to 100 per cent in the groups studied

Etiology. *Morphology* *Enterobius vermicularis* (Linnaeus, 1758) Leach, 1853 [= *Oxyuris vermicularis* (Linnaeus, 1758) Lamarck 1816] is a spindle shaped parasite of man It is usually attached to the mucosa of the lower ileum, cecum or ascending colon The female is 8 to 13 mm long the male 2 to 5 mm The anterior extremity lacks a true buccal capsule but is characterized by three labia and, laterally, a pair of cephalic, winglike alae The mus
bulb (Fig VII 9) The male p
with caudal alae and a single,
tip of the female is distinctly
third of the worm The paired

vulva opening at the base of the "T" near the juncture of anterior and middle thirds of the body The long, clear, pointed posterior end of the female, which is discernible by gross examination, the clear cephalic alae, and the numerous typical eggs within the uteri readily serve to identify this common nematode (Figs VII 8 and VII 9) Adult female pinworms may be recognized in cross sections at appropriate levels by

Figure VII 8



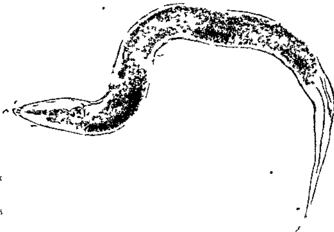


Figure VII 9

Figure VII.8 *Enterobius vermicularis* adult female worms Note shapes and the clear attenuated and pointed posterior end (Courtesy of The Louisiana State University School of Medicine)

Figure VII 9. Adult female *E vermicularis* showing cephalic alae bulb behind esoph agus vulva, egg mass anus and pointed posterior end (Courtesy of The Louisiana State University School of Medicine)

catheter is introduced through the anus about 15 cm From 400 to 500 ml of a 0 2 per cent aqueous suspension of hexylresorcinol are instilled Retention may be facilitated by leaving the catheter inserted and clamping the free end Also the buttocks may be held or taped together The hexylresorcinol suspension should be expelled after retention for one half hour If necessary a small saline enema may be used to initiate expulsion Retention enemas may be repeated at four day intervals for a total of three or four times *if necessary* as indicated by the consistency of the stools

Treatment for Mixed or Multiple Helminthiases Since ascarids and whipworms frequently coexist in the same host dithiazanine iodide is a suitable therapeutic for mixed infections with these two helminths (see pp 403 414) T [illegible]
against ascaria [illegible]
moderate activ [illegible]
choice for the treatment of trichuriasis and strongyloidiasis dithiazanine iodide is of value in treating persons with mixed or multiple intestinal nematode infections which occur so commonly in tropical and subtropical areas

Prophylaxis Prophylaxis depends upon sanitary disposal of human feces washing of the hands before eating avoiding raw vegetables in areas where human excreta are used for fertilizer and supervision of children to prevent dooryard defecation and coprophagy

Enterobiasis

Synonyms Oxyuriasis pinworm or seatworm infection

Definition. Enterobiasis is an infection of the human intestinal tract by the pinworm *Enterobius vermicularis*

Distribution Enterobiasis is a cosmopolitan infection Surveys in various parts of the world indicate that *E vermicularis* is probably the most widely distributed human helminth its incidence varying from 1 to 100 per cent in the groups studied

Etiolo [illegible] *vermicularis* (Linnaeus 1758) L [illegible] (Linnaeus 1758) Lamarck 1816] is [illegible] It is usually attached to the mucosa of the lower ileum cecum or ascending colon The female is 8 to 13 mm long the male 2 to 5 mm The anterior extremity lacks a true buccal capsule but is characterized by three labia and laterally a pair of cephalic winglike alae The muscular esophagus terminates in a distinct bulb (Fig VII 9) The male possesses a strong ventrally curved tail with caudal alae and a single large copulatory spicule The posterior tip of the female is distinctly attenuated constituting the posterior third of the worm The paired reproductive system is "T" shaped the

vulva opening at the base of the T near the juncture of anterior and middle thirds of the body The long clear, pointed posterior end of the female, which is discernible by gross examination the clear cephalic alae and the numerous typical eggs within the uteri readily serve to identify this common nematode (Figs VII 8 and VII 9) Adult female pinworms may be recognized in cross sections at appropriate levels by the bilateral crests and by the eggs within the worm (Fig VII 10)

Females lay embryonated eggs which are flattened on one side, 50 to 60 μ in length and 20 to 30 μ in breadth The shell consists of three parts,

Figure VII 8



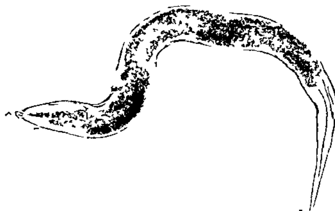


Figure VII 9

Figure VII 8 *Enterobius vermicularis* adult female worms Note shapes and the clear attenuated and pointed posterior end (Courtesy of The Louisiana State University School of Medicine)

Figure VII 9 Adult female *E vermicularis* showing cephalic alae bulb behind esophagus vulva egg mass anus and pointed posterior end (Courtesy of The Louisiana State University School of Medicine.)



Figure VII 10

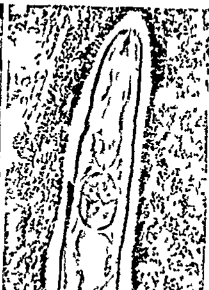


Figure VII 11

Figure VII 10 *Enterobius vermicularis* in lumen of appendix Cross section of adult pinworms shows bilateral crests one worm contains eggs (Courtesy of The Louisiana State University School of Medicine)

Figure VII 11 *Enterobius vermicularis* in lymphatic nodule of appendix Longitudinal section shows prominent bulb behind esophagus (Courtesy of The Louisiana State University School of Medicine)

a thick outer albuminous layer an inner hyaline layer which is thinner and the embryonic membrane An average female produces about 11 000 eggs during the course of her life (Fig VII 2 p 398)

Development Pinworm eggs are infective shortly after being deposited After ingestion the eggs hatch in the upper intestine liberating the larvae which migrate to the region of the ileum moulting twice en route It is not uncommon for migrating larvae to attach themselves temporarily to the folds and crypts of the jejunum and upper ileum Copulation of worms takes place in the lower small intestine the female then migrates into the cecum or lower bowel As their eggs develop the worms

pruritus also serves to liberate the eggs Development from egg to egg requires a minimum period of about 15 days (Fig VII 3)

Epidemiology Pinworm eggs are relatively resistant and withstand desiccation in a humid environment for about ten days Infection occurs by ingestion of the eggs which reach the mouth on soiled hands or in contaminated ... in
fections may ... ns
handling cor ... ay
cause infectic ... an
important factor in autoinfection and maintenance of the primary reservoir (Fig VII 14)

At times retrofection may occur Eggs may hatch in the moist anal region The larvae then enter the large intestine through the anus and mature

Pinworm infection is commonly a group problem affecting families and others living under crowded conditions When one individual in a household is infected, it is usual to find several others also harboring *E vermicularis*

Pathology. *Enterobius vermicularis* produces no significant intestinal pathologic changes Minute mucosal erosions may occur in the immediate vicinity of the worms Pinworms are found occasionally in the wall of the appendix (Fig VII 11) More rarely pinworms migrate through the genital tract of females to the peritoneal cavity, where nodular or granulomatous formations about the worms result

The most important effect is the cutaneous irritation in the perianal region produced by the migrating gravid females and the presence of eggs The intense pruritus causes constant scratching which may lead to dermatitis eczema and severe secondary bacterial infections of the skin

tomatic, the most common symptom is the intense pruritus already described Local symptoms during worm migration vary from mild tickling to acute pain Anorexia, restlessness and insomnia are common in cases of severe involvement The disturbed sleep results in irritability There may be changes in behavior attitudes, including inattention and lack of cooperation Pruritus vulvae and vaginal discharge are not rare Pinworm infection is not a common cause of appendicitis

Diagnosis. Eggs are commonly present in material removed from the perianal skin and, more rarely are encountered under the fingernails or in the feces The most satisfactory method of diagnosing pinworm infections is by the use of a perianal swab The swab utilizes Scotch tape held sticky side out over the end of a tongue depressor, which is then applied to the perianal region The tape is placed sticky side down on a clean glass slide and examined for eggs If desired, a drop of toluene or N/10 sodium hydroxide may be added The swabs should be employed in the morning before the patient bathes or defecates Since children often are bathed before a visit to a physician s office the swabs should be

Treatment Piperazine citrate (Antepar) is the drug of choice This anthelmintic is available in syrup wafer and tablet forms Each milli

grams a day The drug is given in a single daily dose for six consecutive days

Dithiazanine iodide (Delvex, Telmid) is an effective therapeutic for

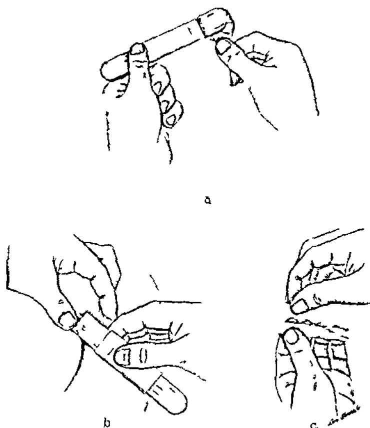


Figure VII 12 Scotch tape slide technique for the diagnosis of enterobiasis a. Tape still partially attached to microscope slide is looped over end of wooden depressor to expose gummed surface b Gummed surface is pressed against several areas of perianal region c Tape is replaced on slide preparatory to examination for pinworm eggs (Adapted from Brooke Donaldson and Mitchell Courtesy of The Louisiana State University School of Medicine)

enterobiasis A dosage for adults of 100 mgm three times daily two hours after meals for five days provided a cure rate of 100 per cent The dosage should be reduced for children Reactions are more frequent in children with this drug than with piperazine Povan pyrvinium pamoate also is an effective therapeutic for pinworm infection

Terramycin has marked anthelmintic activity against *E vermicularis* However, the routine use of broad spectrum antibiotics for the treatment of enterobiasis is not justified

Since pinworm infection frequently is a familial problem it is often desirable when practicable to treat the entire family simultaneously

Prophylaxis Prevention centers around personal hygiene and cleanliness of living quarters Infestation of the household frequently results in reinfection Usually it is not practical to employ many or all of the

prophylactic measures described below. Sleeping clothes, sheets, underwear, towels and wash cloths, folded without shaking, may be soaked in ammonia water (one cup of household ammonia in five gallons of cold water) for one hour or boiled before being laundered. Children may be given a shower bath or stand up bath daily, preferably in the morning, with thorough washing and rinsing of the perianal area and genitalia. Both of the above measures are of particular value during the first few days of treatment. Bathroom fixtures, floor and toilet seat should be cleansed daily, rugs should be vacuumed once a day. Fingernails should be kept short, children should be required to wash their hands before meals and after toileting and to keep their fingers away from the mouth and nose. Metal toys may be sterilized in a hot oven, similar plastic articles may be soaked in the dilute ammonia solution.

Ascariasis

Synonym. Large roundworm infection.

Definition. Ascariasis is an infection by *Ascaris lumbricoides*, one of the most common helminthic parasites of man. The adults commonly remain in the small intestine. Passage of the larvae through the lungs is accompanied by pneumonitis of varying intensity.

Distribution. Ascariasis has a worldwide distribution and is particularly common in regions with poor sanitation or no sanitation. The incidence in some areas of Europe and the Orient is reported to be 90 per cent or more. Highly endemic regions exist in the United States, especially in southeastern parts of the Appalachian range, where 30 to 40 per cent of the population has been found to be infected. It is a common infection, too, in some areas of many southern and Gulf Coast states.

Etiology. *Morphology.* Adult *A. lumbricoides* Linnaeus, 1758 are white, cream or pink in color. They are the largest intestinal nematodes, and their macroscopic appearance is characteristic. The females usually range between 20 and 35 cm. in length, whereas the males vary between 15 and 30 cm. The cuticula is finely striated. The anterior extremity is characterized by three lips, one dorsal and two ventrolateral in position. Each lip carries a pair of small papillae on its lateral border. The male possesses a single set of reproductive organs composed of a long, single, tortuously coiled tubule which is sometimes faintly visible through the cuticula. The copulatory spicules are simple and unequal. The posterior end of the male often is coiled slightly or recurved. The vulva of the female is situated midventrally where the anterior and middle thirds of the body meet. The paired female reproductive system is coiled in the posterior two thirds of the body and, like that of the male, sometimes may be seen through the cuticula. The female produces millions of eggs during her life, laying up to 200,000 per day. Eggs are de-

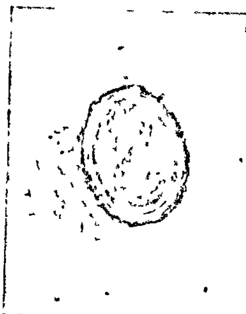


Figure VII 13 Infective egg of *Ascaris lumbricoides* Note larva within the egg (Courtesy of Federico Labbe San Carlos University School of Medicine Guatemala)

posited in an undeveloped stage and may be fertilized or unfertilized The eggs may be covered with an outer roughened (mammillated) albuminous coat if this is lacking the egg is said to be decorticated (Fig VII 2, p 398)

Development The adults live in the lumen of the small intestine especially in the jejunum where they may persist for six months or longer Eggs reach the external environment with the feces Under conditions of sufficient moisture and oxygenation and at an optimum temperature of 25° C, they develop and become infective in about three weeks *Ascaris* eggs develop more rapidly and survive better in shaded soil containing clay than in shaded sandy soil Before eggs become infective for man the contained embryo must have undergone one molt within the egg (Fig VII 13) These eggs hatch in the intestine liberating minute larvae which promptly penetrate blood or lymph vessels in the intestinal wall Some larvae thus reach the portal circulation and are carried to the liver, others pass through the thoracic duct By either route *they must finally reach the lungs where they are filtered out of the blood* stream and in a few days many perforate the alveoli After increasing in size and molting twice the larvae migrate up the respiratory passages to the epiglottis and then down the esophagus In this way the parasites again reach the small intestine where maturation and copulation occur During the migration the larvae increase from about 0 2 to 1 5 mm in length and undergo a total of four molts A new generation of eggs appears in the feces within approximately two months after the ingestion of embryonated eggs (Fig VII 4)

Epidemiology. Children frequently acquire ascariasis by the ingestion of embryonated eggs which reach the mouth by soiled hands or by geophagia Ascariasis often is a dooryard infection (Fig VII 14) Parasitized children who fail to use sanitary facilities contaminate yards with their excrement and thus "seed" the soil with eggs which, upon maturation, provide a source of new infection for others or of reinfection for the original host Uncooked vegetables from gardens which have been

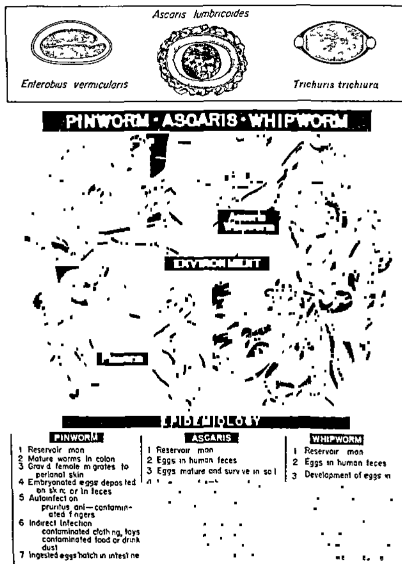


Figure VII 14 Epidemiology of pinworm whipworm and ascaris infections

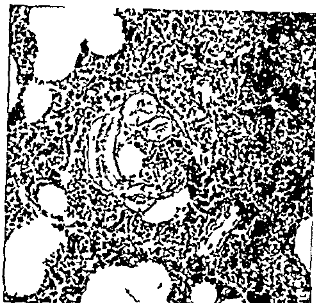


Figure VII 15 Larva of A lumbr co des surrounded by hemorrhage and purulent exuda e in lung Experimental infection in guinea pig

fertilized with human excreta also provide an important source of in fection *Ascaris* eggs are highly resistant to desiccation and to thermal changes under 70° C therefore they may remain infective for a con siderable period Although *A lumbricoides* usually is more prevalent in children this helminth is a common parasite of adults in many areas The magnitude of the global prevalence of ascariasis is attested by Stoll s estimate of 644 million infections which represents more than one fourth of all of man s helminthiases

Pathology *Reactions to Larvae* Minute hemorrhages occur at the penetration sites of the larvae through the intestinal wall and into the alveoli of the lungs In experimental animals exudation of erythro cytes and white blood corpuscles including many eos nophils and des quamation of the pulmonary alveolar epithelium occur (Fig VII 15) Large numbers of infective eggs or repeated ingestion of eggs produce pathologic changes in the lungs characterized by a lobular pneumonitis This is more often seen in ch ldren since they are usually more heavily infected than are adults

Reactions to Adults The adult worms cause no specific pathologic response in the small intestine If however they are present in suffic ent numbers they occasionally form a bolus which produces partial or com

per
ence
etary
cted

by this worm

Clinical Characteristics *Reactions to Larvae* Children are particularly susceptible to ascariasis If numbers of infective eggs are

ingested there may be an elevation of temperature to 103° or 105° F within a period of five days corresponding to the period of migration of the larvae This may be associated with frequent spasms of coughing, bronchial rales, evidence of lobular consolidation and hemoptysis The physical signs often simulate an atypical pneumonia The presence of the parasites is seldom suspected, and thus a clinical diagnosis of *Ascaris* pneumonitis is rarely made Since sputum, when obtainable from the children, usually is not examined for migrating larvae, specific diagnosis is seldom achieved

Reactions to Adults Abdominal pain, frequently colicky in nature and located in the epigastrium or umbilical region, is one of the most common complaints of persons with ascariasis Often a history of passing worms spontaneously is obtained Abdominal distention and tenderness, vomiting and constipation may be present Rarely, allergic reactions to the worms, including dyspnea, may occur *Ascaris* infections often produce no symptoms It is doubtful that ascarids cause convulsions The passing of worms in patients with convulsions is probably due to a migration of ascarids induced by fever of another cause

The most frequent complication of *Ascaris* infection is a partial intestinal obstruction that may proceed to complete obstruction This complication occurs in a small percentage of persons with ascariasis, more often in those with moderate or heavy rather than light infections Although intestinal obstruction sometimes occurs after the onset of a febrile infection, or occasionally after use of some anthelmintics, it may develop without any obvious precipitating factor The usual site of obstruction is the ileocecal region

Diagnosis. Diagnosis depends upon the demonstration of characteristic eggs in the stool or the recovery of an adult worm Recognition of both mammillated and decorticated eggs is important (see Fig VII 2,



Figure VII 16 Ascariasis adults in appendix (Strong Stitt s Diagnosis Prevention and Treatment of Tropical Diseases The Blakiston Co)

p 398) Eggs presenting several different appearances may be encountered in the stool as follows

(1) FERTILIZED EGGS These range from 45 to 75 μ by 35 to 50 μ in diameter Ordinarily they are covered by a coarsely mammillated albuminoid bile stained outer shell beneath which is a thick transparent hyaline inner shell

(2) UNFERTILIZED EGGS These measure 88 to 94 μ by 39 to 44 μ they are longer narrower and have a slightly thinner outer and inner shell than typical fertilized *Ascaris* eggs

(3) DECORTICATED EGGS Occasionally the roughened mammillated outer shell is absent and only the thick hyaline inner shell remains these are known as decorticated eggs They may be fertile or infertile

Ascariasis can usually be detected by direct smears however concentration techniques such as the MGL or AMS III insure a diagnosis (see pp 809–811)

Treatment Piperazine citrate (Antepar) is the drug of choice for the treatment of children and adults for intestinal ascariasis An effective dosage is 150 mgm (hexahydrate equivalent) per kilogram of body weight with a maximum daily dose of 3 grams The drug is given as a single dose and may be repeated a week later if necessary Fasting and purgation are not required The worms are immobilized by the drug but are intact and in a living state when passed This single dose treatment is suitable for mass therapy for ascariasis

Hexylresorcinol (Crystoids anthelmintic) has been employed extensively for the treatment of ascariasis When this drug is to be used a light meal consisting of only soft foods is permitted the night before treatment Crystoids anthelmintic are administered in a single dose with a glass of water the following morning on an empty stomach The pills must be swallowed intact to prevent irritation or burning of the oral tissues Care must be taken that the pills are not retained under the tongue or between the teeth and cheeks No food should be eaten for at least four hours after treatment but water may be taken freely A saline purge (preferably sodium sulfate) should be given 24 hours after treatment Retreatment may be given after an interval of several days if complete removal of the ascarids is not achieved with a single dose For adults and children over 12 years the dose is 1 gram for children 8 to 12 years 0 8 gram 6 to 8 years 0 6 gram up to 6 years of age 0 1 gram

— ll children

425) and

Hetrazan (see p 454) have significant therapeutic value for ascariasis

Partial intestinal obstruction due to *Ascaris lumbricoides* frequently responds to conservative management and surgical intervention may not be necessary in many instances if this method of therapy is followed Parenteral fluids are administered as required If necessary Wangensteen drainage with a Levin tube is employed for abdominal decompression to relieve distention and vomiting Saline enemas are given to remove any worms which may have collected in the large intestine owing to decreased peristalsis However the obstruction is in the small intestine

where the ascarids normally live After four to six hours of nasogastric suction vomiting usually abates and piperazine citrate syrup is instilled by gravity through the tube Suction is discontinued for one to two hours after administration of the drug

The initial dosage of piperazine is 150 mgm per kilogram of body weight with a maximum of 3 grams (30 ml of the syrup) Subsequently 65 mgm of piperazine per kg
given at 12 hour intervals for
drainage is unnecessary the c
cases if the initial dose (150
next dose (65 mgm per kilog
stead of 12) and repeated at 12 hour intervals for six doses After the acute illness has subsided the stools should be examined If eggs of *A lumbricoides* are present the residual infection should be treated with piperazine as an uncomplicated case of intestinal ascariasis

Complete intestinal obstruction in ascariasis requires prompt surgical intervention The prognosis is determined largely by the length of time between onset of the obstruction and the institution of surgical treatment

Prophylaxis Effective prophylaxis against ascariasis as well as trichuriasis consists especially of sanitary disposal of human excreta prevention of fecal contamination of top soil avoidance of eating uncooked vegetables in areas where nightsoil is used as fertilizer and the institu

Hookworm Disease

Synonyms For *Ancylostoma duodenale* infections uncinariasis ancylostomiasis Old World hookworm infection for *Necator americanus* infections necatoriasis New World hookworm infection American hookworm infection

Definition Hookworm disease is an infection of the small intestine by *Ancylostoma duodenale* or *Necator americanus* Tissue destruction and blood loss attributable to the parasites occur in proportion to the abundance of these invaders Malnutrition and avitaminosis aggravate the detrimental effects of infection

Distribution Hookworm disease is widespread and is one of the most important helminthic diseases of man It occurs in nearly all subtropical and tropical countries The estimated number of hookworm infections is 456 millions The ranges of the two species of hookworm infecting man overlap and both are present in many regions

Ancylostoma duodenale the Old World hookworm is prevalent in

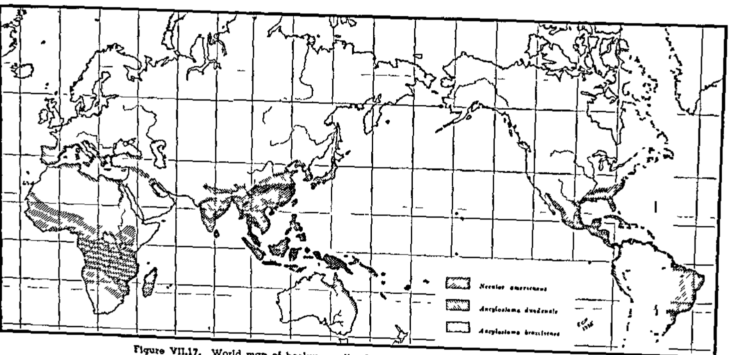


Figure VII.17. World map of hookworm distribution. (Faust & Russell Craig & Faust's Clinical Parasitology, 6th Edition Philadelphia, Lea & Febiger, 1957.)

southern Europe, northern Africa, northern India, China, and Japan, it is also present in southern India, Indonesia, Burma, the Malayan archipelago, the Philippines, south and central Pacific islands, Portuguese West Africa Australia and Paraguay *Necator americanus* is the predominant human hookworm in southern Asia Indonesia, the Philippines, Polynesia, Melanesia, Micronesia, central and south Africa, the southern United States, Central and South America and the West Indies Consult the map in Figure VII 17 for other details

Etiology. *Morphology* *Ancylostoma duodenale* (Dubini, 1843) Creplin, 1845, and *Necator americanus* (Stiles, 1902) Stiles, 1903 cause ancylostomiasis and necatoriasis, respectively Although morphologic differences exist between them, only *A duodenale* will be described here Other important diagnostic differential features are presented in Table VII 1

The adults are pink or creamy white and have a tough cuticula and a pair of prominent cervical papillae that are laterally situated behind the esophageal nerve ring The oval buccal capsule contains, on the ventral (or apparently upper) side, two pairs of fused teeth The outer pair is the larger, the inner is provided with a small, inconspicuous accessory median process (Figs VII 18, VII 19, VII 20, VII 21)

The males are 8 to 11 mm long the females between 10 and 13 mm The posterior tip of the male is expanded to form a typical copulatory *bursa supported by fleshy rays with a pattern that is characteristic of the* species The alimentary canal and genital ducts open into this bursa A pair of long copulatory spicules are regulated by an accessory copulatory device or *gubernaculum*

The females have a subterminal, ventrally located anus on the conical posterior extremity The reproductive system is double, the tubules of the

Table VII 1. Differential Characteristics of Common Hookworms[1]

	NECATOR AMERICANUS	ANCYLOSTOMA DUODENALE	ANCYLOSTOMA BRAZILIENSE	ANCYLOSTOMA CANINUM
Shape	Head curved opposite to curvature of body giving a hooked appearance to anterior end	Head continues in same direction as curvature of body	Similar to *A duodenale*	Similar to *A duodenale*
Length				
Female	9 to 11 mm × 0 35 mm.	10 to 13 mm × 0 60 mm.	9 to 10 5 mm. × 0 38 mm.	14 mm. × 0 6 mm.
Male	5 to 9 mm × 0 30 mm.	8 to 11 mm. × 0 45 mm.	7 8 to 8 5 mm × 0 35 mm.	10 mm × 0 4 mm.
Buccal capsule	One pair of ventral semilunar cutting plates	Two pairs of curved ventral teeth of nearly the same size rudimentary inner pair	Two pairs of ventral teeth inner smaller	Three pairs of ventral teeth inner smallest
[illegible]	[illegible]	[illegible]	[illegible]	Opening large oval long axis dorsoventral
[illegible]	[illegible]	[illegible]	[illegible]	Large and flaring, with long slender rays
Caudal spine in female	Absent	Present	Present	Present
Vulva	Anterior third to middle of body	Posterior to middle of body	Posterior to middle of body	Posterior to middle of body
Size of eggs (microns)	64 to 76 × 35 to 40	56 to 60 × 35 to 40	55 to 60 × 34 to 40	60 to 75 × 38 to 45

[1] From Belding Textbook of Clinical Parasitology New York Appleton-Century Crofts, Inc., 1952, p. 285

Figure VII 18



Figure VII 19





Figure VII 20



Figure VII 21

Figure VII 18 Mouthparts of *Necator americanus* Note two pairs of chitinized cutting plates characteristic of this species (Courtesy J M Edney through A O Foster)

Figure VII 19 Mouthparts of *Ancylostoma duodenale* Note two large pairs of teeth each of the medial pair bearing a small accessory process (Courtesy J M Edney through A O Foster)

Figure VII 20 Mouthparts of *Ancylostoma braziliense* Note two pairs of teeth a large outer pair and a small inner pair without accessory processes (Courtesy J M Edney through A O Foster)

Figure VII 21 Mouthparts of *Ancylostoma caninum* Note three well developed pairs of teeth (Courtesy J M Edney through A O Foster)

ovary being coiled intricately over the alimentary canal and confined to the posterior two thirds of the body The vulva is located ventrally at the beginning of the posterior third of the body During copulation the copulatory bursa of the male surrounds the vulva thus giving the spermatozoa access to the reproductive system of the female After mating the male becomes detached Fertilization takes place in the upper portion of the uterus or in the seminal receptacle

Differential diagnosis of the various species of hookworms depends upon their length the number and arrangement of the teeth or cutting plates the length of the esophagus the detailed morphology of the bursa of the male the position of the vulva in the female and the size of the

eggs Table VII 1 summarizes these points in tabular form for the two common hookworms of man and for two closely related species

Development Since the life cycles of these two species are essentially identical they will be considered together Adult hookworms live

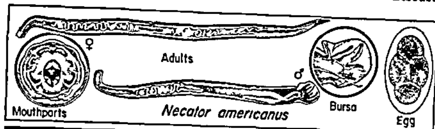
hatch within 24 to 48 hours each liberating a rhabditiform larva approximately 250 to 300 μ long Its anterior extremity is bluntly rounded and is characterized by a long narrow buccal cavity Hookworm larvae in this stage of development may be confused with the rhabditiform larvae of *Strongyloides* (see Table VII 2) The rhabditiform larvae of the hookworm may migrate several inches beneath the soil where they feed on bacteria molt gradually double in size and finally undergo a metamorphosis to become infective or filariform larvae During this period of growth a second molt or ecdysis occurs the parasites frequently remaining within their sheaths

The worms then enter a period during which no food is consumed but active vertical migration may continue When these infective larvae come into contact with unprotected human skin they penetrate the superficial layers enter the blood stream and are transported to the lungs There they leave the vascular system emerge into the alveoli and migrate up the bronchi and trachea and down the esophagus to reach the small intestine where maturity is attained Eggs appear in the stool five or more weeks after invasion of the host by the larvae (Fig VII 5)

Epidemiology The infective filariform larvae ordinarily enter the skin As penetration is difficult mud caked on the foot or between the toes gives the larvae a purchase for the actual penetration

In the tropics coffee and banana groves and sugar cane and sweet potato fields are ideal for the growth and development of the larvae Conditions most favorable to embryonic development include a loose moist shaded sandy soil loam or humus through which the filariform larvae are able to crawl vertically They cannot however climb up rocks or the sides of concrete lined latrines Temperatures ranging between 80° and 90° F are optimal Because eggs and larvae are readily killed by freezing and desiccation hookworm disease is endemic only in those tropical and subtropical areas where the rainfall averages 50 or more inches a year (Fig VII 22)

In many parts of the world special habits or customs of the people are factors in maintaining hookworm infections In some regions for example there are usually certain defecation areas which adults use These spots often provide the proper environment for the development of infective hookworm larvae Adults revisit these sites daily thus exposing themselves to infection and reinfection Young children often defecate beside the house or in the area in which they play In other parts of the world such as China dissemination is furthered by the utilization of un



HOOKWORM

Anemia — Cachexia

Eggs passed in feces

Penetration of skin by larvae

EPIDEMIOLOGY

1. Fecal contamination of soil
2. Rhabditiform larvae in soil
3. Filariform larvae on soil
4. Penetration of exposed skin
5. Migration of larvae
6. Localization, small intestine
7. *Feeding on blood of host*
8. Eggs passed in stool

Filariform larva

Rhabditiform larva

Figure VII 22 Epidemiology of hookworm disease

treated nightsoil as fertilizer Infection results as the fields are worked

There is a fundamental distinction between hookworm infection and hookworm disease the two terms are not synonymous and the medical implications are quite different It is difficult to obtain adequate data on the incidence and distribution of hookworm disease The method for routine stool examination merely demonstrates the presence of the para

site it provides no exact evidence of the magnitude of the hookworm burden Other methods involving egg count techniques give data on the *intensity* of the infection thus furnishing a basis for estimating the worm burden of an individual Persons harboring hookworms may be divided into two groups

(1) The hookworm "carrier —a person with few worms and no clinical evidence of hookworm disease

(2) The clinical case—a patient carrying many worms who presents clinical evidence of hookworm disease Clinical cases are severe only

States and certain other areas it does not conform to the findings in Okinawa Southern Korea and Japan where the incidence increases until old age is reached and the individuals cease working in fields contaminated by nightsoil In many areas men may be more heavily infected than women but in Okinawa South Korea and Japan this is not true the incidence is approximately the same but the *worm burden* is higher in women

It appears probable that some human immunity to hookworm develops otherwise large numbers of people would die from the disease The incidence is lower and heavy infections are less often encountered in Negroes than in whites Knowledge of the development of immunity is based upon experimental studies made with the dog hookworm It has been found that small repeated infections give almost complete immunity When such immunity develops the worms in the gut are eliminated anemia however may prevent the development of immunity Further experiments demonstrate that preexisting malnutrition and avitaminosis determine the appearance of hookworm disease after doses of worms that ordinarily would produce only a subclinical infection If immunity has been established it can be lost if the diet becomes deficient it can likewise be restored after an adequate diet has been resumed This immunity to the invasion of the larvae seems to be a response to their secretions and excretions the mechanism of which is the formation of precipitates which are deposited around the larvae Their motion is then slowed and they soon disintegrate and are phagocytosed

There is also evidence of a gradual and spontaneous reduction in the numbers of hookworms in cases where there is no reinfection It has been estimated that in *N americanus* and *A duodenale* infections there is a 70 or more per cent reduction of the worm burden within one or two years and a total elimination by the end of five to 15 years

Pathology The penetration of the skin by the filariform larvae of *Necator americanus* often causes a *local dermatitis* "ground" or "dew itch" with edema erythema and a vesicular or papular eruption which usually subsides spontaneously in about two weeks unless secondary bacterial infection occurs *Ancylostoma duodenale* however seems much less prone to produce a cutaneous reaction

As the migrating larvae leave the capillaries of the lungs and penetrate into the alveoli minute *hemorrhagic lesions* are produced In heavy



Figure VII 23 Longitudinal section through hookworm attached to intestinal mucosa.

infections these may be numerous and may be accompanied by round cell infiltration In general however the pulmonary reaction often is not evident clinically or is mild

The adults of both human species inhabit the upper half of the small intestine where they become attached and suck blood (Fig VII 23) Of these *N americanus* is believed to be the more benign Injury to the host results from the mechanical and lytic destruction of tissue at the point of attachment A secondary hemorrhagic anemia is the chief pathologic condition It has been estimated that a single hookworm may remove as much as 0 38 to 0 84 ml of blood a day When this figure is multiplied by thousands of worms and repeated day after day for long periods the resulting anemia is readily understood Hookworms digest only part of the blood they ingest Previous points of attachment bleed for some time after the worm moves on to a new site owing to the anticoagulant secreted by the worm

Clinical Characteristics The clinical picture of hookworm disease is variable and depends primarily upon the severity of the infection and the diet of the individual Common symptoms are weakness fatigue dyspnea on exertion cardiac palpitation pallor epigastric discomfort and in heavy infections of long duration mental and physical retardation Children harboring this parasite in large numbers are frequently pot bellied Aberrations of appetite such as a craving for earth (geophagy) wood charcoal or other abnormal substances are not unusual Advanced cases with severe anemia and hypoproteinemia may present extensive edema and cardiac damage

In many areas where the infection is heavily endemic malnutrition is widespread in the population Furthermore the clinical picture may

be complicated by concurrent malaria and other parasitic infections of the intestinal tract Hookworm disease therefore seldom appears as a clear cut entity The most serious effects occur in children (Fig VII 24), however, blood loss from hookworm infection can influence health and productivity and may even prove fatal in adults

The anemia of hookworm disease may be severe with hemoglobin values under 15 per cent and erythrocyte counts below 1,000 000 per cubic millimeter The cells are usually microcytic and hypochromic However, when the disease is complicated by malnutrition the anemia may be macrocytic or normocytic in type

There may be a moderate leukocytosis more commonly the total white blood count is within normal limits A moderate increase in eosinophil percentage may exist It is less marked however, in advanced cases

As noted above penetration of the skin may be associated with a severe pruritus

Diagnosis Diagnosis depends upon finding typical eggs in the stool (Fig VII 2, p 398) Differentiation between the eggs of *N americanus* and *A duodenale* is not necessary or possible It is important however, that the rhabditiform larvae of hookworm, *Strongy*

distinguished

it is usually

okworm and

Strongyloides, since those of *Trichostrongylus* and *Rhabditis* are rarely encountered Rhabditiform larvae of hookworm will occasionally be found in stool samples which are held too long before examination The

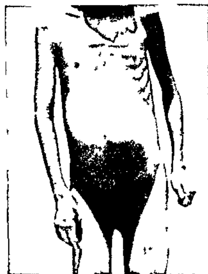


Figure VII.24 Clinical hookworm disease showing emaciation and protuberant abdomen (Maj D S Glusker M.C. A U.S., for the Office of the Coordinator of Inter American Affairs)

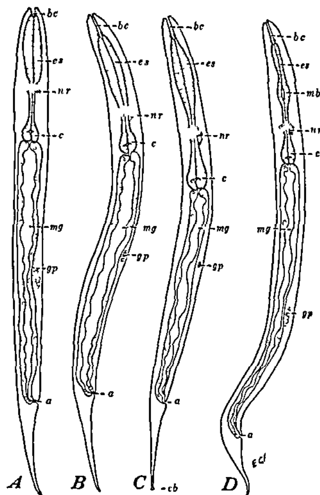


Figure VII 25 Figures of typical rhabditoid larval stages of A *Strongyloides* B hookworm C *Trichostrongylus* and D *Rhabditis* ca 400 × Explanation of labels *a* anus *bc* buccal chamber *c* cardiac bulb of esophagus *cb* beadlike swelling of caudal tip *es* esophagus *gp* genital primordia *mb* midesophageal bulb *mg* mid gut *nr* nerve ring (Courtesy of E. C Faust. In Faust and Russell, Clinical Parasitology Phila delphia Lea & Febiger 1957)

presence of embryonated eggs and rhabditiform larvae in the stool is suggestive of hookworm infection or mixed infections of hookworm and *Strongyloides stercoralis* If only rhabditiform larvae are present strongyloidiasis should be suspected It should be borne in mind that mixed infections are common, especially in the tropics Rhabditiform larvae of hookworm and *S stercoralis* may be differentiated by the characteristics listed in Table VII 2

Stools should be examined by direct smears and by some concentration method such as the MGL, AMS III or zinc sulfate techniques (p 809)

Table VII.2. Rhabditiform Larvae

CHARACTER	STRONGYLOIDES	HOOKWORM
Size average	225 × 16 μ	275 × 17 μ
Posterior tip	Blunter	Sharper
Buccal chamber	Short or absent	Long
Genital primordia	Larger	Smaller

If it is desired to determine the worm burden, the Stoll technique sho[illegible] be utilized (p 812)

Differential Diagnosis Hookworm disease may be confused w[illegible] wet beriberi, malarial cachexia, chronic nephritis and with anemias [illegible] other etiology Both beriberi and malaria may coexist with hookwo[illegible] disease and complicate the diagnostic and the therapeutic probl[illegible]

Treatment. TETRACHLOROETHYLENE In hookworm infections [illegible] complicated by ascariasis the drug of choice is tetrachloroethylene [illegible] dose of 0 10 or 0 12 ml per kilogram of body weight (maximum of [illegible] in a single dose) is highly effective for the removal of hookworms T[illegible] anthelmintic is administered in the morning on an empty stomach [illegible] food is withheld for several hours afterward No purgative is given [illegible] or after treatment When the drug is administered without purgation, [illegible] is tolerated better by anemic patients and is more effective in [illegible] of worms Two or more treatments at four day intervals may be nece[illegible] sary to achieve complete removal of the worms If eggs are found [illegible] in concentration techniques, either initially or after one or more [illegible] of tetrachloroethylene, treatment or retreatment may not be [illegible] This regimen has been employed safely and effectively [illegible] therapy and for patients with severe anemia Transient [illegible]

[illegible]

(Alcopara Alcopar) has made available an additional [illegible] for hookworm infection The standard dosage, regardless of [illegible] is 5 grams of the hydroxynaphthoate salt, which contains [illegible] the bephenium base The anthelmintic is available in [illegible] which are shaken in one half glass of water and taken [illegible] dose in the morning on an empty stomach No food is [illegible] least two hours after treatment Purgation is not [illegible] remove the drug before the full anthelmintic effect is [illegible]

For mass treatment for hookworm infection a [illegible] bephenium has been recommended For hospitalized [illegible] larly when persistent diarrhea is present, more [illegible] obtained with three doses each of 5 grams of [illegible] granules given in one day, or a daily dose of 5 [illegible] days Side effects from bephenium therapy [illegible] borygmi, nausea and vomiting

MIXED HOOKWORM AND ASCARIS INFECTIONS [illegible] with hookworm and Ascaris occur, bephenium [illegible] therapeutic An alternate method of treating [illegible]

fections with hookworm and *Ascaris lumbricoides* involves the elimination of the ascariasis by means of a short and intensive regimen of *piperazine citrate* *This is followed by treatment with* tetrachloroethylene without purgation The widely quoted view that the presence of ascariasis contraindicates the use of tetrachloroethylene is not concurred in by *many physicians*

A combination of 600 mgm of dithiazanine and 1 gram (for a child) or 2 grams (adult dose) of tetrachloroethylene on three alternate days has been employed to treat mixed helminthiases, including coexistent hookworm and *Ascaris* infections This results in a 97 to 100 per cent reduction of the hookworm egg count, removal of the ascarids, and frequently the elimination of other coexisting intestinal nematode infections A similar dose once weekly for three weeks has also been employed

In mixed infections with hookworms and ascarids, it also has been a common practice to employ hexylresorcinol (Crystoids anthelmintic see page 414) This anthelmintic is active against both helminthiases but is less effective against hookworm than tetrachloroethylene After the ascarids have been removed, the patient may be treated with tetrachloroethylene to eliminate or further reduce the hookworm burden

Supportive Measures Anthelmintic treatment may need to be supplemented or preceded by the administration of ferrous sulfate, the institution of an adequate, balanced diet, and, in some cases with extreme anemia by transfusion with whole blood or packed red corpuscles Generally, removal of the worms an improvement of the diet and administration of iron are sufficient

Prophylaxis. The prophylaxis of hookworm infection is based upon sanitary disposal of human excreta and the prevention of soil pollution In heavily endemic areas it is usually necessary to carry out mass treatment of the population to reduce the reservoir of infection, to construct adequate latrine facilities, and perhaps of even greater importance, to instruct the population concerning the epidemiology of the infection and the necessity for the prevention of soil pollution The wearing of shoes to prevent contact of exposed skin with infested soil is one of the most important preventive measures An adequate, balanced diet containing sufficient iron to permit compensation for blood loss will prevent or reduce clinical manifestations

Trichostrongyliasis

Synonym *Trichostrongylus* infection

Definition. Trichostrongyliasis is an infection caused by one of several species of *Trichostrongylus* Adult worms lie with their heads embedded in the mucosa of the duodenum and jejunum

Distribution Although several species that normally parasitize lower animals have been reported in isolated instances to affect man in various parts of the world it is only *Trichostrongylus orientalis* which has been found as a common intestinal parasite in certain areas of Armenia Japan Korea Formosa and China In some areas of Japan *Trichostrongylus* sp is the most common helminth encountered Tricho strongyliasis has also been reported from Chile

Etiology *Morphology* Adult *Trichostrongylus* sp are small roundworms the males measuring 4 to 6 mm in length and the females 5 to 8 mm The head is unarmed a distinct buccal capsule is absent but a definite notch occurs where the excretory pore opens Males are char acterized by a copulatory bursa with rays and spicules that are diagnostic for each species In the female the paired reproductive system opens through a common vulva The eggs are elongate oval possess a trans parent hyaline shell and resemble those of hookworms except that they are much larger (85 to 115 μ) When found in the feces they are usually in the morula stage (Fig VII 2)

Development Under favorable conditions of humidity and tem perature the eggs hatch within 24 to 36 hours However they are remark ably resistant to long periods of cold or drought The larvae undergo two ecdyses and reach the infective stage in 60 hours or more Infection normally occurs when infective larvae are ingested although adult parasites have been recovered following penetration of the skin They mature in the small intestine within 25 to 30 days without undergoing a migration through the lungs

Epidemiology Man is believed to acquire the infection through contaminated food or drink The universal use of nightsoil in the Orient and the resistance of eggs and infective larvae to desiccation often create conditions in farming communities which are ideal for the spread of *Trichostrongylus* Herbivorous animals are common reservoir hosts

Pathology and Clinical Characteristics Little is known concern ing the pathology of trichostrongyliasis In severe infections a mild anemia dry skin and general emaciation have been reported In Japan significant clinical phenomena were not observed even in individuals

should be taken to avoid confusion of *Trichostrongylus* eggs with those of hookworm since tetrachloroethylene is not very active against trichostrongylids

Treatment *T orientalis* infections reportedly are eliminated with 300 to 600 mgm of dithiazanine iodide daily for three to six days A single dose of piperazine adipate gave a 74 per cent cure rate of *Tricho strongylus* infections

Prophylaxis Effective prophylaxis against trichostrongyliasis in volves the sanitary disposal of human excreta and the prevention of fecal contamination of the topsoil by infected animals or man

Strongyloidiasis

Synonyms Strongyloidosis *Strongyloides stercoralis* infection the strongylid threadworm

Definition *Strongyloidiasis is an infection by the nematode S stercoralis* the female of which usually is embedded in the mucosa of the small intestine of man

Distribution Strongyloidiasis occurs primarily in the tropics and subtropics although it has been reported sporadically from temperate regions

Etiology *Morphology* The parasitic adult female *S stercoralis* (Bavay, 1876) Stiles and Hassall 1902 is minute about 2 mm long The cuticula is delicately striated and the esophagus occupies one third to two fifths of the body length The paired ovaries oviducts and uteri open through a short vaginal orifice near the beginning of the posterior third of the body The mature parasitic female lies buried in the mucosa

larvae are 200 to 250 μ long and closely resemble the rhabditiform larvae of hookworm differing from them chiefly in having a shorter buccal capsule a larger genital primordium and a more robust posterior extremity (Table VII 2 p 425)

The little known parasitic male is about 0 7 mm long It possesses two spicules and a gubernaculum but no caudal alae The tail is pointed and ventrally curved It is similar morphologically to the free living adult male observed in strains with an indirect cycle

Development The ecology of *S stercoralis* is complex Several cycles are known The *direct* form of development is most common In *this cycle rhabditiform larvae are passed in the stool* Under favorable environmental conditions they transform in soil into filariform larvae within 24 hours These infective larvae are capable of penetrating the intact skin of man

Less commonly an *indirect* cycle is observed in which rhabditiform larvae develop into free living adult males and females The latter de*posit eggs in the soil the eggs in turn develop into rhabditiform larvae* These may transform directly to the filariform stage or into free living adults Under suitable conditions repeated generations of free living adults may develop thus continuing the indirect cycle for a limited period Ultimately infective filariform larvae are produced

The infective filariform larvae of *S stercoralis* resemble hookworm *larvae at the corresponding stage of development* but are smaller and possess a much longer esophagus and a tail with a minute notch which is diagnostic The filariform larvae which penetrate the skin eventually reach the lymphatics or capillaries and are carried to the right side of the heart and the pulmonary capillaries Here the larvae leave

the capillary beds and penetrate into the alveoli of the lungs The parasites then migrate u[illegible]
pass down into the
in the duodenum or
the mucosa to oviposit, thus completing the life cycle

The prepatent period is about one month Since the parasitic adult male *S stercoralis* has been seen only rarely, it is believed that the parasitic female may be parthenogenetic, like an analogous species, *S ratti*, in rats

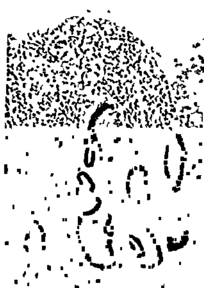
In certain cases the cycle is completed entirely within the host Rhabditiform larvae in minute fecal particles which remain in the perianal region after defecation can transform readily into filariform larvae These penetrate the perianal skin, producing a form of hyperinfection referred to as *external* or *perianal autoinfection* A fourth developmental cycle is *internal autoinfection* The rhabditiform larvae that ordinarily would be passed into the stool rapidly metamorphose into dwarf filariform larvae within the bowel These directly penetrate the mucosa of the colon and rectum

The above two types of hyperinfective cycles provide a built-in mechanism by which the patient's worm burden can be increased or replenished, even though he may never again come in contact with infested soil It can easily be seen that, once acquired, such an infection can be continued for years—even for life—and that, protected by favorable internal environmental conditions, it can persist in any climate Repeated autoinfection results in the pyramiding of one generation of adult parasites upon another in the duodenum, this process probably accounts for the frequent recurrences of clinical episodes which characterize this disease

Epidemiology. While much remains to be learned concerning the epidemiology of strongyloidiasis, it is known that man usually acquires the infection by skin contact with the infective filariform larvae Penetration is effected in the same manner as in hookworm infection

Pathology. Penetration of the skin usually causes no marked reaction Larvae which reach the blood stream are carried to the lungs, where they migrate into the alveoli Presumably they cause some bleeding as they erupt from the pulmonary capillaries and excite cellular infiltration On rare occasions a scattered patchy kind of infiltration (Loeffler's pneumonia) may occur in this infection In general, pulmonary pathologic changes in human strongyloidiasis are not marked The maturation of *S stercoralis* to the adult stage in the lungs has been demonstrated in an experimental host If this occurs in humans, it must be extremely rare Occasionally, hyperinfective filariform larvae en route to the intestine may be found in sputum This has been observed prin-

duodenum and upper jejunum There, they invade the mucosa (Fig VII.27), but ordinarily do not go below the muscularis mucosae Less frequently they may be found in the mucosa of the pyloric region of the



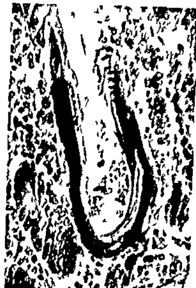


Figure VII 26 Figure VII 27

Figure VII 26 Embryonated eggs of *Strongyloides stercoralis* in mucosa of duodenum. (Courtesy of The Louisiana State University School of Medicine)

Figure VII 27. Portion of a parasitic adult female *S stercoralis* in mucosa of small intestine (Courtesy of The Louisiana State University School of Medicine)

stomach or ileum The females soon produce eggs singly or in nests near the bases of the villi and in the interglandular stroma (Fig VII 26) Upon hatching the young larvae gradually work into the lumen of the intestine In heavy infections the mucosa may be honeycombed by both the adult worms and the hatched larvae In some cases, the reaction to the infection results in a duodenitis, which may be detected radiographically An eosinophilia of about 10 per cent is usual, occasionally patients are seen with eosinophil percentages in excess of 50 per cent due to strongyloidiasis

Clinical Characteristics. The symptoms of strongyloidiasis vary In some patients the parasite produces moderate or severe gastrointestinal disturbances, in others the infection may cause no symptoms *The clinical manifestations relate primarily to the duodenitis* Pain in the midepigastrium is the most common complaint It is often sharply localized to the right of the midline, does not radiate, and may be described as a burning sensation, a deep dull ache or a cramp The ingestion of food or alcohol may increase the pain When the pain is localized tenderness to deep firm pressure frequently is present A salient diagnostic combination is the presence of pain in the epigastrium together with eosinophilia

Nausea and vomiting may begin when the pain appears A tentative diagnosis of peptic ulcer is often made in patients with strongyloidiasis Diarrhea, anorexia weight loss, weakness and generalized urticaria are relatively common complaints Clinical exacerbations recur at irregular

intervals and may be due to hyperinfection Strongyloidiasis is a chronic disease and may lead to invalidism Fatalities have been reported in persons with massive hyperinfection but are exceedingly rare

Diagnosis Eosinophilia is the most characteristic feature of the blood picture polymorphonuclear leukocytosis may be marked or absent

Examination of several stool specimens may be necessary to demonstrate larvae The finding of motile rhabditiform larvae in a stool is highly suggestive of strongyloidiasis Confirmation may be made by carefully checking the morphology of the larvae to distinguish them from those of hookworm The rhabditiform larvae of *Strongyloides* possess a short buccal capsule The formalin ether (MGL or AMS III) techniques usually reveal larvae if they are in the feces (see page 809 for details of the methods) Eggs of *S stercoralis* are observed in stools only on extremely rare occasions

In about one fourth of the cases of strongyloidiasis the larvae will not be found in the stool If an infection with this parasite is suspected aspirated duodenal fluid may be examined for the presence of larvae (Fig VII 25) and embryonated eggs (see page 803 for method) after examination of several stools has failed to demonstrate larvae

Treatment The introduction of dithiazanine iodide (Delvex Telmid) has provided an effective therapeutic agent for strongyloidiasis The dosage of dithiazanine for adults is 100 mgm three times daily two hours after meals for two or three weeks

Prophylaxis The prophylaxis of strongyloidiasis does not differ from that of hookworm disease In both the essential features are prevention of soil pollution by human feces and protection against infection by the wearing of shoes

47

Tissue-Inhabiting Nematodes

The Filarioidea

Biology of the Filarioidea

Introduction Nematodes principally inhabiting the extraintestinal tissues of man include the filarial worms the guinea worm the trichina worm and larvae of several other species of nematodes normally parasitic in animals such as the dog and cat hookworm and ascarids and the gnathostomes These belong to the superfamilies FILARIOIDEA DRACUNCULOIDEA TRICHURIOIDEA STRONGYLOIDEA ASCARIDOIDEA and SPIRUROIDEA Only parasites in the first subdivision will be considered here

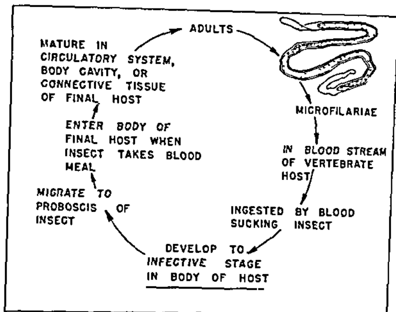


Figure VII 28 *Nematode cycle—filarial worm type*

Members of the Filarioidea infecting man may be characterized as follows (1) The threadlike adults inhabit the tissues or body cavities of a vertebrate where the females produce eggs which are partially or completely embryonated (2) At the time of oviposition or just prior thereto the embryos uncoil and are known as microfilariae (3) The eggshell may persist accommodating itself to the elongated larva thus producing a "sheathed microfilaria If the shell ruptures a naked or "unsheathed" microfilaria results (4) All microfilariae must pass a developmental stage in a blood sucking insect vector (Fig VII 28)

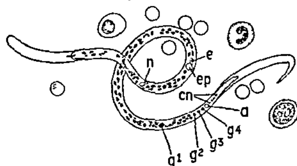
Some of the tissue inhabiting nematodes produce diseases in man Thus Bancroft s filariasis is an infection by *Wuchereria bancrofti* filariasis malayi by *W malayi* onchocerciasis by *Onchocerca volvulus* and loiasis by *Loa loa* Two other filariae *Acanthocheilonema perstans* and *Mansonella ozzardi* which are found in man do little if any damage and produce few if any symptoms In addition to these well recognized parasites a number of rarer forms have also been reported in man but will not be considered here

Morphology of the Filarioidea

Adults The adult parasites vary between 19 mm and 60 cm in length the females often being twice as long as the males Most are creamy white filiform worms whose cuticle may be smooth transversely striated or covered with annular rings or knoblike bosses There are species–specific papillae about the head mouth and usually the tail In some species the males possess caudal alae and all have spicules which vary in size and shape Further details will be found in the discussion of the appropriate species

Microfilariae Adult females produce prelarvae known as microfilariae which range from 177 to 300 μ in length Some of these embryonic forms retain their shells as "sheaths" others break out and hence are "unsheathed" Sheaths appear as delicate close fitting membranes that may be detected only where they project beyond the head or tail of the microfilariae Internally each parasite is seen to consist of columns of nuclei which are believed to represent the anlagen of various systems

Figure VII.29A.



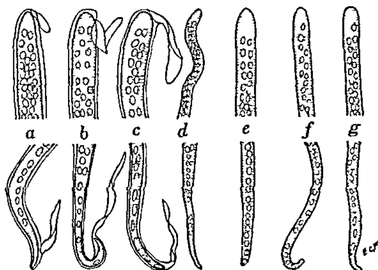


Figure VII.29B

Figure VII.29A. Diagram of an unsheathed microfilaria of *Wuchereria bancrofti* from peripheral blood showing characteristic features *a* anal pore *cn* caudal nuclei *e* excretory cell *ep* excretory pore *g1–4* genital cells *n*, nerve ring (Original.)

Figure VII.29B Differential characteristics of head and tail ends of the microfilariae of *a* *Wuchereria bancrofti*, *b* *W malayi* *c* *Loa loa* *d* *Onchocerca volvulus* *e* *Acanthocheilonema perstans* *f* *A streptocerca* and *g* *Mansonella ozzardi* Greatly enlarged drawn to scale (Faust and Russell Clinical Parasitology Philadelphia Lea & Febiger 1957)

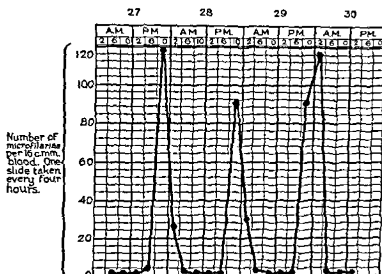


Figure VII.30 Periodicity of *Wuchereria bancrofti* in peripheral blood (After Manson Bahr in Strong Stitt's Diagnosis Prevention and Treatment of Tropical Diseases The Blakiston Company)

and structures The best means of differentiating various species of microfilariae lies in noting the position of organ precursors of parts of the digestive, excretory and reproductive systems and the position of the caudal nuclei These stain deeply with hematoxylin and occupy characteristic positions Certain anatomic landmarks differ in their distances from the anterior tip of the worm Such structures include the nerve ring, excretory pore, excretory cell in relation to the excretory pore, anal pore and the four genital cells, G_{1-4} (Fig VII 29)

A determination of the type of periodicity displayed by the microfilariae is of value in making tentative species identifications, although periodicity can be reversed in some species if the patient works at night and sleeps during the day For example, the microfilariae of the nocturnally periodic form of *W bancrofti* occur in greatest numbers in the peripheral blood between 8 P M and 2 A M while the microfilariae of the diurnal or "no

day and night (Fig

filariae are diurnal

known It may be associated with a migration of the microfilariae to the peripheral circulation from the small vessels in the lungs where in some filarial species, they are found in large numbers during the daytime

Developmental Stages. All members of the FILARIOIDEA require an insect intermediate host As this vector feeds on man, microfilariae are ingested The parasites soon leave the vector's alimentary canal undergo a period of development in the thoracic muscles and finally migrate into the mouthparts, where they are infective for man When the insect next feeds on man the parasites leave the vector, penetrate the skin surface and migrate to the internal site sp... for the development

Table VII 3 Vectors of Human Filarioidea

PARASITE	HOSTS
Wuchereria bancrofti and *Wuchereria malayi*	Many species of mosquitoes belonging to the genera *Culex Aedes Mansonia Anopheles*
Onchocerca volvulus	Black flies *Simulium damnosum Simulium neavei Eusimulium avidum Eusimulium ochraceum Eusimulium mooseri* and probably others
Loa loa	Tabanid flies *Chrysops dimidiata Chrysops silacea*
Mansonella ozzardi	Midge *Culicoides furens*
Acanthocheilonema perstans	Midge *Culicoides austeni Culicoides grahami*

of the given species of worm After maturing and mating the adult females produce microfilariae (Fig VII 29) The better known vectors are listed in Table VII 3

Differentiation of Microfilariae Microfilariae in onchocerciasis may occur in aspirate of nodules in thin sections of skin or in tissue fluid obtained by the skin scarification technique Microfilariae of other species of the FILARIOIDEA are found in films of the peripheral blood *some being diurnal others nocturnal Still others display no periodicity* These larvae or prelarvae may be differentiated by the key presented in Table VII 4

A more detailed summary of the microfilariae infecting man occurs in Table VII 5

Table VII 4 A Key to the Common Microfilariae Infecting Man

1 (10)	Microfilariae in peripheral blood	2
2 (7)	Microfilariae sheathed	3
3 (4)	Nuclei do not extend to tip of tail cephalic space equal to diameter of head nocturnal periodicity (or nonperiodic ?)	*Wuchereria bancrofti*
4 (3)	Nuclei extend to tip of tail in broken or unbroken chain diurnal or nocturnal periodicity	5
5 (6)	Nuclei extend in solid row to tip of tail diurnal periodicity	*Loa loa*
6 (5)	Nuclei extend in broken row to tip of tail resembling *W bancrofti* except for two small terminal nuclei cephalic space twice diameter of head nocturnal periodicity	*Wuchereria malayi*
7 (2)	Microfilariae unsheathed	8
8 (9)	Nuclei extending to tip of tail often appearing as a double row	*Acanthocheilonema perstans*
9 (8)	Nuclei not extending to tip of tail	*Mansonella ozzardi*
10 (1)	Microfilariae in skin and subcutaneous tissues nuclei not to tip of tail	*Onchocerca volvulus*

Table VII.5. The Differentiation of the Microfilariae of the Filarioidea of Man*

SHEATHED MICROFILARIAE FROM PERIPHERAL BLOOD

Characteristics	*Wuchereria bancrofti*	*Wuchereria malayi*	*Loa loa*
Periodicity	Usually nocturnal	Nocturnal	Diurnal
Appearance	Graceful sweeping curves	Stiff, secondary kinks	Stiff, secondary kinks
Tail	Tapers to a delicate point, terminal nuclei absent	Slight bulb at tip, 2 terminal nuclei	Gradual tapering, caudal nuclei continuous row into tail
Length	244–296μ (thick films)	177–230μ (thick films)	250–300μ (thick films)
Excretory cell	Small, near excretory pore	Large, far behind excretory pore	Large, far behind excretory pore
G cells	Small, similar in size, G_2–G_4 far G_1, G_1–70 14	Larger, G_1 relatively [illegible]	Similar to those of W [illegible] G_1–68 6%‡
Anal pore	82 48%		
Intermediate host	Best—*Culex fasciatus* (= *Culex fatigans*), *A gambiae*	*Anopheles spp*	
Cephalic space	As long as broad	Twice as long as broad	?
Stylets	1	2	?
Body nuclei	Well defined	Blurred, intermingled	Larger and stain less deeply

UNSHEATHED MICROFILARIAE FROM PERIPHERAL BLOOD

Characteristics	*Mansonella ozzardi*	*Acanthocheilonema perstans*
Stylet	1	0
Tail	5 terminal nuclei not reaching tip of tail	Nuclei extend to tip of tail, often in 2 rows

MICROFILARIA OF SKIN AND SUBCUTANEOUS TISSUES

Characteristics	*Onchocerca volvulus*
Sheath	Absent
Stylet	None
Tail	Curved
Nuclei	5–7 near tip

* Modified from Faust's adaptation from Feng 1933

† Subgenus *Mansonoides*

‡ Distance from anterior end

Filariasis Bancrofti

Synonyms Bancroft s filariasis *Wuchereria bancrofti* infection

Definition Filariasis bancrofti is due to the presence of adult *W bancrofti* in the lymphatic system or connective tissues of man The infection may be accompanied by important pathologic conditions related to the lymphatic system including inflammatory lesions dilatation and rupture of lymphatics hypertrophy hyperplasia and fibrosis Offspring of the parent worms known as microfilariae are characteristically present in the circulating blood their presence while alive does not contribute to the pathologic changes listed above Many species of *Anopheles Culex Mansonia* and *Aedes* are vectors

Some workers regard periodic filariasis bancrofti as different from the diurnal or nonperiodic form Variations in the clinical development of these two entities their mutual geographic isolation and their different types of periodicity suggest the possibility that two species or perhaps varieties of etiologic agent exist The name *W pacifica* has been proposed for the diurnal or nonperiodic form

Distribution The periodic or classic form of filariasis bancrofti is widespread throughout the tropics and subtropics except in the southwest Pacific (Fig VII 31) In the western hemisphere it was formerly established as far north as Charleston S C but has become extinct there The disease occurs throughout the West Indies Colombia Venezuela Panama and the coastal portions of the Guianas and Brazil

In Europe it appears to be limited to Spain (Barcelona) and Turkey along the North African Coast it occurs spottily from lower Egypt to Morocco Other areas include a wide belt across the central portion of Africa Madagascar the neighboring islands and the east coastal region

The disease is endemic in the Orient In many localities its distribution overlaps that of *W malayi* which was not described until 1927 The periodic form has also been reported from coastal Arabia to India and is found with the Malayan form in India southeast Asia southern China the Philippines and southern Japan Although both are generally present filariasis malayi predominates in Sumatra Borneo Celebes and Ceram in Indonesia but not in New Guinea or tropical Australia

The diurnal or nonperiodic type of filariasis bancrofti appears restricted to the islands of the South Pacific area

Etiology *Morphology* Adult *W bancrofti* (Cobbold 1877) Seurat 1921 localize in the lymphatic vessels and the lymph nodes *The males and females are often closely intertwined* The mature worms are threadlike cylindrical and creamy white with a smooth cuticula and bluntly tapering extremities The slightly swollen cephalic region bears two rings of small papillae The unarmed mouth opens directly into a cylindrical esophagus which is divided into an anterior muscular and a posterior glandular portion The male worm can be as long as 40 mm On the ventrally curved tail may be found a maximum of eight preanal and four postanal pairs of papillae supporting narrow inconspicuous

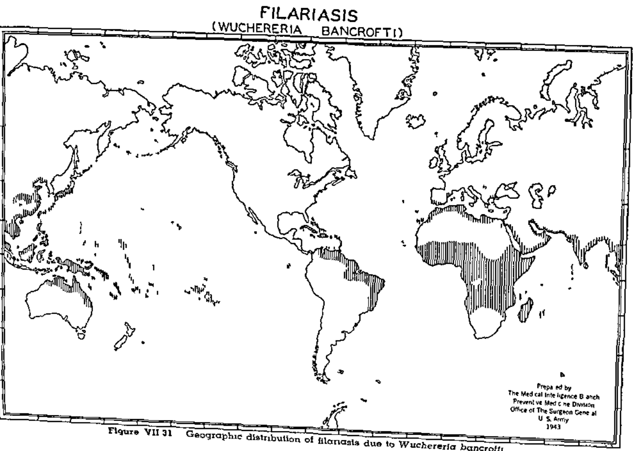


Figure VII 31 Geographic distribution of filariasis due to *Wuchereria bancrofti*

alae farther caudad there are two pairs of larger papillae and one pair of smaller ones Copulatory spicules which vary in size and shape and a crescent shaped gubernaculum characterize the male

The females are longer ranging between 80 and 100 mm The vulva opens about 0 8 or 0 9 mm from the anterior tip The vagina extends to a long bilateral coiled uterus which has its origin about 1 mm from the posterior tip

Developing microfilarial embryos are coiled in a membrane or shell averaging about 38 by 25 μ in size Later this structure elongates to form the microfilarial sheath

Fully developed sheathed microfilariae measure 244 to 296 μ in length by 7 5 to 10 μ in breadth The tip of the head is described as bearing a stylet and the cephalic space between the column of nuclei and the anterior tip is approximately equal to the diameter of the head Adequate staining of smears is necessary to determine that the nerve ring is 20 per cent of the body length from the anterior tip the excretory pore 29 6 the excretory cell 30 6 the G_1 cell 70 14 and the anal pore 82 4 per cent (see Fig VII 29A) The last 5 per cent of the body length the tail is devoid of nuclei a point of importance in distinguishing between the microfilariae of this species and *W malayi* (see Table VII.5) Microfilariae of periodic and nonperiodic *W bancrofti* are morphologically indistinguishable

Development Adult *W bancrofti* normally inhabit the lymphatics where they liberate microfilariae The latter either remain in the lymph or reach the peripheral circulation where they are ingested by the mosquito vector as it feeds They complete their intermediate development in the gut and tissues of the insect host

Within an hour after ingestion the larvae exsheath and those that are not passed in the mosquitos feces penetrate the stomach wall and migrate within 24 hours to the thoracic muscles Here the parasites undergo a series of complex morphologic changes including two molts During this period the developing larvae pass from a sausage shaped stage to mature infective filiform (third stage) larvae between 1 4 and 2 mm in length Under optimum conditions ten to 11 days are required for this transformation to occur The larvae then migrate to the mouthparts of the mosquito from which point they reach the new host when the mosquito next feeds Since the larvae usually leave the mosquito by breaking through Duttons membrane it is believed they actively penetrate the skin entering either the puncture site or possibly even forming their own portal of entry The filiform larvae which succeed in establishing entrance eventually reach the lymphatic system and are thought to mature within about a year The details of the migrations and development of these worms within man are not fully known

Epidemiology Complete development of the larval forms of *W bancrofti* has been shown to occur in over 50 species of mosquitoes included in the genera *Anopheles Culex Aedes* and *Mansonia* However these mosquitoes are not all necessarily concerned with the transmission of the infection in nature Some of the most important known vectors are *C pipiens quinquefasciatus* (*C fatigans*) *C pipiens Anoph*

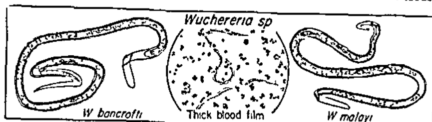


Figure VII 32. Epidemiology of filariasis

eles gambiae, A funestus, A darlingi, A punctulatus, A farauti, Aedes aegypti and *Aedes polynesiensis*

The importance of a particular mosquito will depend to a large extent upon whether it feeds on human rather than animal blood and breeds in areas in close proximity to man The conditions necessary for maintaining filariasis at a high level of endemicity are an adequate human

reservoir a sufficient number of cases having numerous microfilariae in the peripheral blood and ample breeding of suitable mosquitoes within range of the infected population Since some vectors are daytime feeders and others purely nocturnal the infection may be transmitted by day as well as by night in certain areas (Fig VII 32)

The roles of occasional or continuous infection in the development of the syndromes of the disease are not known It is said that the incidence of demonstrable infection is low in young children and infants and highest after the twentieth year It is also said that the prevalence of clinical disease varies between the sexes in different parts of the world This may be an expression of differences in occupation of the infected individuals and of variations in the behavior and habitats of the important vectors in different regions It is probable that persons experiencing asymptomatic infections and the early clinical stages of the disease constitute the important human reservoir In the early or advanced stages particularly in the presence of elephantiasis microfilariae may not be present in the peripheral blood

As previously indicated periodicity is the alternate increase and decrease in the number of microfilariae present in the peripheral blood The epidemiologic importance of the phenomenon of periodicity is that it will determine which species of mosquito become infected Microfilariae with nocturnal periodicity are therefore transmitted almost exclusively by night biters while nonperiodic microfilariae are carried by any suitable species regardless of its time of feeding

There is no natural immunity to human filariasis

Pathology The essential pathologic changes in filariasis consist of inflammatory reactions and subsequent progressive obstruction of lymphatic channels by scar tissue These changes occur especially in the vicinity of adult worms which are commonly found in the lymphatic vessels especially those of the abdominal cavity However worms may be present in the lymphatics in any part of the body Common sites are the elephantoid tissues of the external genitalia and the mammary gland the lymph nodes of the extremities and the retroperitoneal tissues particularly about the kidneys There is no evidence to indicate that circulating microfilariae participate in the production of lesions (Fig VII 33)

Biopsy studies performed on United States troops in the Southwest Pacific infected by the nonperiodic W *bancrofti* during World War II have thrown some light on the genesis and the progression of the pathologic changes The acute stages of filariasis of the lymphatic system may occur as early as three months after exposure Essentially the same lesions were found whether or not adult worms living or dead were present Furthermore there was no indication that either microfilariae or bacteria participate in the early pathology

The lesions in the lymph nodes were characterized by granulomatous inflammation proliferation of the macrophage (reticuloendothelial) system and eosinophilia of adjacent tissues The dilated sinuses showed a wide zone of macrophages with variable numbers of eosinophils lymphocytes and foreign body giant cells at the periphery Necrosis was

Table VII.6. Some Known and Probable Vectors of *Wuchereria bancrofti* by Countries

Region	Country	Vectors
AFRICA.	Belgian Congo	*Aedes aegypti* *Anopheles funestus* *Anopheles gambiae*
	Central Africa	*Mansonia uniformis*
	Egypt	*Culex pipiens quinquefasciatus* *Culex pipiens*
	Liberia	*Anopheles gambiae* *Anopheles melas* *Anopheles hancocki*
	Mauritius	*Anopheles gambiae* *Anopheles funestus*
	Nigeria	*Aedes ochraceus*
	Sierra Leone	*Anopheles squamosus squamosus* *Anopheles funestus* *Anopheles gambiae* *Anopheles rhodesiensis*
	Tanganyika	*Culex pipiens quinquefasciatus*
	Tunisia	*Anopheles algeriensis*
	West Africa	*Aedes aegypti* *Anopheles funestus* *Anopheles gambiae*
	Zanzibar	*Culex pipiens quinquefasciatus* *Anopheles funestus* *Anopheles gambiae*
ASIA.	China	*Culex vagans*
	Central China (Shanghai area)	*Culex pipiens* *Culex pallens* *Anopheles pipiens sinensis*
	South China	*Culex pipiens quinquefasciatus*
	India	*Culex pipiens quinquefasciatus* *Culex vagans* *Culex vishnui* *Mansonia annulifera* *Anopheles annularis* (= *A. fuliginosus*) *Anopheles barbirostris barbirostris* *Anopheles pallidus* *Anopheles philippinensis* *Anopheles stephensi* subsp *Anopheles subpictus subpictus* (= *rossi*) *Anopheles sundaicus* *Anopheles vagus vagus* *Anopheles varuna* *Anopheles ramsayi* (= *A. pseudojamesi*)

Table VII 6 (Cont'd)

Travancore	*Anopheles n ger mus*
Japan	*Culex p p ns* *Culex p piens pallens* *Culex s nens s* *Aedes togoi* *Anopheles s nens s*
Phil pp nes	*Culex p p ens qu nquefa cia u*
Formosa	*Culex p p ens qu nquefasciatus*
Okinawa	*Culex p p ens qu nquefasciatus* *Culex tritaen orhynchus* (?) *Anopheles s nensis*
A STRALIA New S uth Wales	*A d s a gypti*
Q eensland	*Anopheles am ctus*
General	*Culex p p ens qu nquefasciatus* *Aedes r o lax*
ENTRAL PACIFIC ISLANDS Indones a	*Aedes tongae* *Culex fuscocephalus* *Culex u h tmorei*
ENTRAL PACIFIC ISLANDS Indones a	*Culex annul ost s* *Culex al s* *Culex b taen o hynchus* *Culex s ens* *Culex t ita n orhynchus* *Aed r g lax* *Man on a annulata* *Manson a ind ana* *Manson a d es* (= *M long polp s*) *Manson a un form s* *Anopheles acon tus* *Anophel s bancrof i*
(also Kabaena Is)	*Anoph les ha ker*
Solomon Islan ls	*Anoph les faraut* and related species
Certa n Indones an Islands	*Culex qu nqu fasc atus* (= *C fat gans*) *Culex vishnu* *Anoph les n gers mus*
S UT PACIFIC ISLANDS	*Aedes scutella s* *Aed s tongae* *Anopheles kol ens s*
Celebes (East Ind es an l other Pacif c Islan ls)	*Culex p p ens qu nqu fasc atus* *Anophele acon tus* *An ph les bancrof* *Anoph les macula us* *Anopheles farauti* *An ph les pun tula us*



Figure VII 35 Filariasis fibrotic reaction about partially calcified worms in the capsule of a lymph node

of the skin and subcutaneous tissues and the development of elephantiasis

Clinical Characteristics The infection may produce no symptoms in some persons while in others a variety of manifestations may ensue The clinical phases of filariasis may be classified as inflammatory or obstructive The effects of inflammation may include lymphangitis lymphadenitis orchitis epididymitis funiculitis filarial abscess, elephantoid fever and secondary bacterial infections especially by streptococci and staphylococci The obstructive phase is accompanied by a variety of clinical syndromes Lymphatic dilatation without rupture produces lymph varices lymph scrotum and hydrocele Rupture of the distended lymphatics is responsible for chyluria and chylous ascites The advanced stages of the obstructive phase are characterized by elephantiasis which commonly affects the leg the scrotum the arm and the mammae

Clinical filariasis normally has a prolonged incubation period which *is seldom of less than eight to 12 months duration* and may be much longer However it is now well established that clinical phenomena may appear within three months of exposure The early stages of the infection are usually accompanied by inflammatory phenomena and fever which frequently suggest other conditions

The initial symptoms are largely local and unaccompanied by significant constitutional reaction They usually consist of pain swelling or redness of an arm or leg or pain and swelling in the scrotal region Stiffness of an involved extremity is common Local lymphangitis with enlargement of the regional lymph nodes particularly the epitrochlear the axillary *the femoral or the inguinal nodes* depending upon the site



Figure VII 36 Filariasis thickened spermatic cord



Figure VII 37 Filariasis varicose inguinal lymph nodes (After Taniguchi Kumamoto in Strong Stitt s Diagnosis Prevention and Treatment of Tropical Diseases The Blakiston Company)

of infection frequently accompanies the early symptoms Fever is usually mild when present Characteristically the acute local symptoms are transitory rarely persisting more than a week or ten days Enlargement of lymph nodes however tends to persist Repeated recurrences of these phenomena are usual in the early stages of the disease

The Inflammatory Phase *Acute lymphangitis* is a common early manifestation usually involving the lower extremities accompanied by fever ranging from 101° to 104° F often with chills and by more or

less severe toxemia The onset is frequently preceded by a "focal spot" of sharply circumscribed pain and tenderness often in the region of one of the malleoli and followed by ascending lymphangitis originating in this area In other instances the lymphangitis begins centrally and follows a centrifugal course The affected part is swollen often tender and painful and the involved lymphatics are frequently palpable The skin may be diffusely reddened or red streaks may be seen over the inflamed lymphatic vessels When the abdominal lymphatics are involved the clinical picture may suggest malaria or an acute abdomen Involvement of the testes and spermatic cord is common Spontaneous resolution occurs after several days The skin of the affected part may return to normal or there may be residual induration Recurring attacks are usual

Inguinal lymphadenitis commonly accompanies or may precede filarial lymphangitis The nodes are usually enlarged painful and tender during the attack

Filarial orchitis is a frequent acute manifestation The onset is usually sudden with pain in the testicle fever and occasionally rigors The testicle enlarges rapidly and is extremely tender, this condition is commonly accompanied by hydrocele Recurrences are frequent.

Funiculitis, a lymphangitis of the spermatic cord and *epididymitis* are likewise common complications of filariasis (Fig VII 36)

Filarial abscesses are often deeply seated in intermuscular fascial planes but frequently occur about infected lymph nodes particularly those of the inguinal axillary and epitrochlear regions Dead filarial worms may be present in the abscess cavity The pathologic process apparently is the combined result of the presence of the parasite and secondary bacterial infection

Elephantoid fever is a recurrent acute febrile condition which may be associated with elephantiasis or lymphangitis Inflammatory phenomena may be absent in these instances it is probable that there is an acute lymphangitis of the visceral lymphatics The onset is usually sudden with fever ranging from 102° to 104° F rigors and sweating An attack may last from a few hours to several days Recurrences are common and often frequent

The Obstructive Phase This phase of filariasis is characterized by interference with the lymphatic circulation edema and accumulations of serous fluid These manifestations frequently appear in the course of the various phenomena of the inflammatory phase which commonly leave evidence of progressive lymphatic obstruction in their wake. The two phases of the disease therefore often exist concurrently each contributing to the progressive pathologic changes

Lymph varices or "varicose glands" commonly affect the inguinal or femoral lymph nodes of one or both sides and less often the axillary nodes These are soft lobulated swellings which usually develop slowly as the result of obstruction and dilatation of the lymphatic vessels They are not attached to the overlying skin The dilated lymphatics are palpable and tense having a soft elastic consistency The condition is usually painless and insidious Aspirated fluid may contain microfilariae Incision may be followed by a persistent lymph sinus (Fig VII 37)

n many instances is associated with inguinal lymph
r n occurs with fever swelling

be present in this ...

Hydrocele is a frequent accompaniment of ... It may develop
common localization of adult worms in the epididymis It may develop
acutely in the course of filarial orchitis or epididymitis or more slowl
and with relatively few local symptoms Microfilariae are often demon
strable in the serous fluid

Chyluria is the result of obstruction and dilatation of the thorac
duct or its chyle carrying tributaries followed by rupture of distende
lymphatics into the urinary tract and the appearance of chyle in th
urine The urine frequently has the appearance of milk Blood is oft
present in varying amounts giving a pinkish coloration On standin
the urine separates into an upper fatty layer a semitransparent gelatino
... and a pinkish sediment containing lymp
... d by pain in the back
... ever may be present
aching in the lower ... Recurrences are usual and th
attack commonly lasts only a few days Recurrences are usual and th
are intermissions of varying duration



Figure VII.38



Figure VII.39

... elephantiasis of legs and breasts. Cook Island
... edema of leg

Elephantiasis occurs particularly in the legs and scrotum and less frequently in the arms mammae or vulva as a late complication of filariasis It appears in only a small percentage of infected persons The complication develops gradually in the course of repeated attacks of acute filarial lymphangitis in adults exposed for many years to reinfection of the lymphatics by the parasites The skin and subcutaneous tissues are greatly thickened and fibrotic and the regional lymph nodes draining the affected area are usually enlarged In the majority of cases of elephantiasis microfilariae are not demonstrable in the blood (Figs VII 38 VII 39)

Diagnosis In the early stages of filariasis microfilariae may not be demonstrable in the peripheral blood and the diagnosis must be based on clinical data alone A history of exposure in an area of known endemicity of an incubation period of at least three months duration prior to the appearance of symptoms and of recurrent inflammatory phenomena is highly suggestive

Certain objective signs should be carefully sought Commonest of these is enlargement of the regional lymph nodes draining the affected area with or without swelling of an extremity or of the scrotal contents The spermatic cord is frequently thickened indurated and nodular Hydrocele of moderate degree is common even in the early stages of the disease and there may be enlargement of the testicle as well

There is at present no laboratory test which provides dependable diagnostic criteria in the absence of demonstration of the microfilariae Complement fixation tests using antigen prepared from related worms (*Dirofilaria immitis*) have not proved to be reliable However skin tests using antigen from adult *D immitis* or from microfilariae of *W bancrofti* have given few false reactions even during the preclinical stage of the disease

Although adult worms may be present in affected lymph nodes biopsy is emphatically contraindicated since it further augments lymphatic obstruction Between acute inflammatory attacks subjection of the individual to heavy physical exertion often initiates an acute recurrence accompanied by characteristic clinical phenomena The acute episodes are co

In

strate

phases and in the stage of advanced elephantiasis A thick film of fresh blood is useful in light infections since the actively motile microfilariae are easily found Stained thick smears should be used in preference to thin films Smears of the sediment from laked centrifuged blood should be used when other methods fail When infection by nocturnally periodic forms is suspected blood for examination should be taken at night preferably after nine o clock Day time specimens are preferable for the diurnally periodic form (Fig VII 40) Airborne spores of saprophytic fungi such as m lumbricoides may contaminate blood films be mistak fied as microfilariae

filariae es be demonstrated in fluid aspirated from

cele or nodes

See page 454

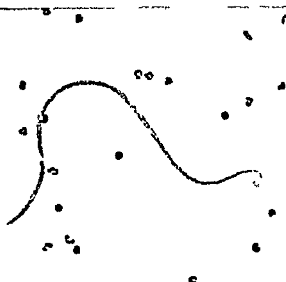


Figure VII.40 Microfilaria of *W bancrofti* in thick blood film stained with hematoxylin to show sheath and characteristic tail. (Courtesy National Institutes of Health U.S.P.H.S.)

Filariasis Malayi

Synonyms Brug's filariasis *Wuchereria malayi* infection

Definition Filariasis malayi is due to the presence of adult *W malayi* in the lymphatics lymph nodes or connective tissues of man Characteristic sheathed microfilariae occur in the peripheral blood only at night Species of *Mansonia* are of particular importance as vectors In other respects this disease is fundamentally similar to filariasis bancrofti

Distribution Filariasis malayi is found in India Vietnam China Korea Japan Indonesia and Malaya The following areas are known as endemic centers for Brug's filariasis Malaya India–Travancore Vietnam–Delta of the Red River China–Huchow and Changsha Indonesia–Celebes Borneo Ceram Java Sumatra It has also been found among the Tonkinese in the New Hebrides and among Koreans in Hawaii (Oahu) It appears to be the only filarial worm found in Korea and it also has been reported among Japanese on a coastal island off Honshu In some areas the distribution of *W malayi* and *W bancrofti* overlaps (see Fig VII.41)

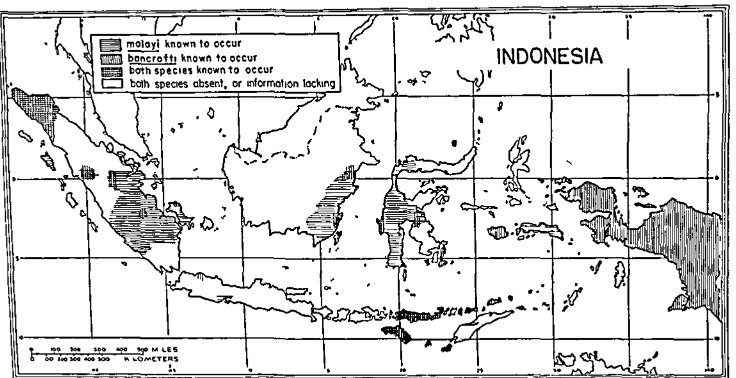


Figure VII.41 Distribution of filariasis in Indonesia. (Courtesy Preventive Medicine Division Bureau of Medicine and Surgery U S Navy)

iology *Morphology* Filariasis malayi is caused by the filarial
asite *W malayi* (Brug, 1927) Rao and Maplestone 1940 which
ars a close resemblance to *W bancrofti* The adults are white delicate
orms that occur coiled and paired in the dilated lymphatics Two rows
small papillae surround the mouth The males are smaller, 22 to
3 mm in length and their posterior extremities undergo about three
complete loops The cloaca is 0 1 to 0 14 mm from the posterior tip
There is a large pair of papillae near the cloaca and one posteriad and
two other smaller pairs are nearby The copulatory spicules are unequal
in length and a small naviculate gubernaculum is present The known
females are about 55 mm long by 0 16 mm in diameter The vulva is
situated 0 92 mm from the anterior end the anal pore is 0 94 mm from
the posterior tip Although the measurements made by Dutch and Indian
scientists are in essential accord the descriptions of the papillae differ in
dicating the desirability of further morphologic observations

The sheathed microfilariae of *W malayi* are 177 to 230 μ in length and
5 to 6 μ in breadth There is an anterior cephalic space about twice as
long as the diameter of the head the latter bearing double stylets Stain
ing reveals that an excretory pore is situated 30 09 per cent of the body
length from the anterior tip the large excretory cell 37 07 per cent the
G_1 cell 68 83 per cent and the anal pore 82 28 per cent The body tapers
from the anal pore the column of large nuclei terminating some distance
before the acuminate tip of the tail is reached The distal extremity is
swollen to accommodate a single distinct nucleus a second smaller one
lies a short distance anteriad The position of these nuclei and the length
of the cephalic space constitute the two characteristic features of this es
sentially nocturnal microfilaria (see Table VII 5 p 436)

Development The development cycle parallels that of *W ban
crofti* in all essential details The microfilaria of this species undergoes
two molts and completes its development in the mosquito in six days
under optimum conditions

Epidemiology Although the epidemiology is very similar to th
of filariasis bancrofti certain differences exist in the identity and ecolo
of the vectors and in the periodicity of the microfilariae The genera
accepted mosquito vectors belong to the genera *Mansonia* (subgenus *M
sonioides*) and *Anopheles* The known and suspected vectors are s
marized by countries in Table VII 7

The *Mansonia* group constitutes a difficult larval control problem
cause these organisms secure their oxygen by attaching themselv
such green aquatic plants as *Pistia* spp or water lettuce *Eichh
crassipes* or *Lemna* sp In Travancore India filariasis malayi was re
by removing the water plant *P stratioides* on which the larvae
principal vector *Mansonioides annulifera* lived Ordinarily lar
measures such as the use of oil Paris green or DDT are ineffec

The microfilariae are essentially nocturnally periodic Altho
are present in the peripheral blood nearly 20 hours a day
reached about 4 A M thus differing from the condition note
turnally periodic filariasis bancrofti

Recently it has been shown that the domestic cat may be
bstantiated it is possible that an animal is at h

Table VII.7. Known and Suspected Vectors of *Wuchereria malayi* by Countries

China	*Anopheles hyrcanus sinensis*
India	*Mansonia annulifera*
Indonesia	*Mansonia annulata* *Mansonia annulifera* *Mansonia indiana* *Mansonia longipalpis* *Mansonia uniformis* *Anopheles barbirostris barbirostris*
Japan	*Anopheles hyrcanus sinensis*
Malaya	*Mansonia annulata* *Mansonia annulipes* *Mansonia longipalpis* *Mansonia uniformis* *Mansonia indiana* *Anopheles letifer* *Anopheles barbirostris* *Anopheles hycranus sinensis* *Anopheles umbrosus*
Philippines	*Mansonia annulata*
South Korea	*Anopheles hyrcanus sinensis*
Vietnam	*Mansonia indica*

perimental laboratory studies Successful transmission was also obtained in the long tailed *Macaca rhesus* monkey

Pathology and Clinical Characteristics. The pathologic changes and the clinical syndromes associated with infections by *W malayi* range from asymptomatic adenitis to periodic attacks of fever and lymphangitis, and to elephantiasis typically involving the feet and legs Elephantiasis of the upper limbs is seldom seen Lymph scrotum chyluria and chylous hydrocele have not been observed, and elephantiasis of the genitalia is rare Treatment as outlined for filariasis in general is indicated

Diagnosis. The diagnosis rests upon a clinical picture suggestive of filariasis and its confirmation by the demonstration of characteristic microfilariae of *W malayi* (see p 802) The morphology of the sheathed microfilaria differs from that described for *W bancrofti* chiefly in the cephalic space which is twice as long as broad and the posterior extremity of the worm, which has a slight bulb at the tip with two minute terminal nuclei, the remainder of the tapering posterior extremity is devoid of nuclei (Fig VII 42) Skin tests may be of value if microfilariae cannot be demonstrated

Treatment of Filariasis Bancrofti and Malayi. Diethylcarbamazine (Hetrazan Notezine, Banocide) rapidly decreases the number of microfilariae or eliminates them from circulating blood Clinical and bi

psy evidence indicates that the drug also probably has a direct effect on the adult worms

Side reactions following the administration of Hetrazan are common but usually are not serious or of sufficient intensity to require termination of therapy The reactions include fever, malaise vertigo urticaria headache nausea vomiting and inflammatory reactions of the lymph nodes and the scrotal contents Delayed reactions consisting of bullous eruptions and abscess formation occasionally result Hetrazan is non toxic The reactions appear to be allergic responses to the products of the parasites following institution of therapy rather than to the drug itself

The bullous reactions sometimes seen in persons after administration of diethylcarbamazine for filariasis can be arrested promptly by a combination of cortisone and prednisone Corticosteroids must be given with extreme caution to patients with secondary bacterial infections

For the treatment of individual cases of filariasis bancrofti a dosage of 2 mgm per kilogram of body weight three times daily after meals for three or four weeks usually produces permanent elimination of circulating microfilariae and causes the ultimate death of adult worms Dosage of 0 3 to 2 mgm per kilogram three times a day for two or three weeks have been employed relatively successfully for the treatment of filariasis malayi Concurrent administration of an antihistaminic drug may lessen the incidence and severity of the allergic reactions

For mass therapy for filariasis bancrofti 3 mgm per kilogram of body weight are administered in a single dose once a month for 12 to 18 months Unsupervised mass treatment with diethylcarbamazine is not considered practicable in endemic areas of filariasis due to W *malayi* owing to the marked clinical reactions which would occur in the microfilaria carriers

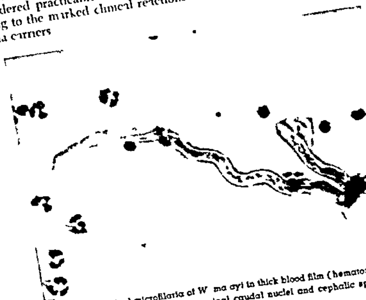


Figure VII.42. Sheathed microfilaria of W ma ayi in thick blood film (hematoxylin Note position of characteristic terminal caudal nuclei and cephalic space

The administration of 100 mgm of cortisone daily in divided doses for a month or longer to patients with elephantiasis may be followed by reduction or disappearance of induration by diuresis and an increase in the number of circulating microfilariae The induration reappears after therapy is discontinued through gradually decreased doses but some degree of improvement may persist for several months Retreatment with smaller doses of cortisone for short periods as relapses occur seems beneficial

Treatment of filarial lymphangitis with antibiotics is without direct effect Antihistaminics are beneficial for symptomatic treatment of this manifestation but acetylsalicylic acid is more effective in reducing pain and fever

Hydrocele may be treated satisfactorily by injections of sclerotic agents such as sodium psylliate and sodium morrhuate

Chyluria should be treated by complete bed rest the foot of the bed should be elevated Cystoscopic treatment and bladder irrigations may be required in severe cases when more conservative measures fail

Surgical procedures are completely contraindicated except for definitive treatment of elephantiasis especially of the scrotum Palliative operations directed to improve lymph circulation in elephantiasis of the extremities are seldom successful Such conditions are best managed by a period of continuous elevation of the affected part An elastic stocking or elastic bandage must be worn constantly afterward In cases of early elephantiasis of the lower extremities elevation and pressure bandages are particularly successful in reducing the swelling Care must be taken not to bandage too tightly and the limb must be exercised to prevent venous stasis In mild cases the leg may assume its original size and the skin a natural texture remaining normal for a prolonged period without further treatment

a suspensory and

The essential features of prophylaxis against filariasis are mosquito control and individual protection against possibly infected mosquitoes (pp 442–444) The different breeding areas and times of flight of the various species that may serve as vectors are complicating factors Since certain of the vectors are daytime transmitters and others nocturnal mosquito infested communities in endemic regions should be avoided Transmission of W *bancrofti* in some areas such as American Samoa is primarily in the bush along trails and on plantations transmission within villages is relatively unimportant This renders prophylaxis and control more difficult

Specific control measures applicable to a particular area will depend upon locally important mosquito vectors In regions where a suitable species of *Mansonia* (*Mansonioides*) is prevalent the problem is difficult The breeding of this group cannot be readily controlled since the larvae secure their oxygen by attaching to the stems of floating aquatic plants such as *Pistia* or water lettuce Consequently the use of oil or surface application of Paris green or DDT is ineffective Removal of the aquatic vegetation or the introduction of minnows are the only satisfactory meas

ces the former has been quite successfully carried out experimentally Mass treatment of infected population groups with Hetrazan therapy 2.0 mgm per kilogram of body weight) may prove to be a useful and practical measure in some regions to reduce the prevalence of the infec tion Such mass treatment significantly reduces both the number of per sons having microfilariae in the circulating blood and the number of in fective mosquitoes thus diminishing the cycle of transmission

In highly endemic areas a combination of treatment sanitation and use of insecticides offers the greatest likelihood of success in the control of filariasis

Onchocerciasis

Synonyms Onchocercosis "blinding filarial disease"

Definition. Onchocerciasis is due to the presence of the filarial parasite *Onchocerca volvulus* in the skin subcutaneous and other tissues of man where it may produce fibrous nodules Blindness is a serious complication of this infection The disease is transmitted by species of buffalo gnats or black flies of the family SIMULIIDAE.

Distribution. In the Western Hemisphere onchocerciasis is largely confined to Mexico and Central America although cases have been re ported from Venezuela and Dutch Guiana It is widespread in tropical Africa In the Americas it occurs principally among persons inhabiting the western slope of the Sierras at altitudes of 600 to 2000 meters Guate mala and the southern states of Mexico constitute the chief endemic cen ters In Africa onchocerciasis is found from Sierra Leone and Liberia southward through the Gold Coast Dahomey Nigeria and the Came roons to the Congo then east to the southern Sudan Uganda Nyasaland Kenya Tanganyika and Kavirondo (Fig VII 43) Recently it has been reported in southern Arabia

Etiology *Morphology* The adult parasite *Onchocerca volvulus* (Leuckart 1893) Railliet and Henry 1910 (= *Onchocerca caecutiens* [Brumpt 1919]) occurs in tumors in the subcutaneous connective tissu The living parasites are white or cream colored and transparent with cuticula showing distinct striations Both extremities are blunt An teriorly about the mouth are two concentric circles of four papillae ea In addition there is a pair of large oral lateral papillae situated betw these two circles Posteriorly the tightly coiled males show copul spicules and a number of perianal and caudal papillae which altho diagnostic nevertheless show considerable variation in position males are 19 to 42 mm long and the females 33 to 50 cm The vul the female opens posterior to the esophagus Microfilariae of sizes 285 to 368 by 6 to 9 μ and 150 to 287 by 5 to 7 μ are produ

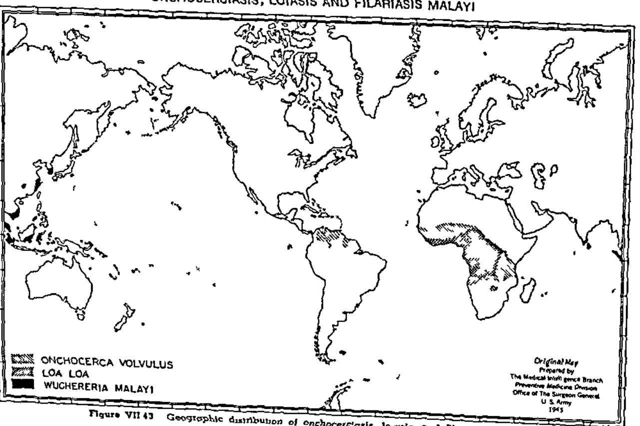
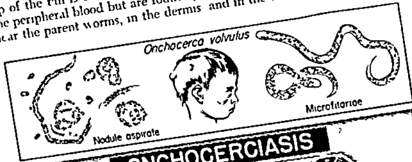


Figure VII 43 Geographic distribution of onchocerciasis loiasis and filariasis malayi

Development. The microfilariae of *O. volvulus* probably exsheath soon after leaving the female worm. Both extremities and the excretory pore region of these larvae lack nuclei. The absence of nuclei from the tip of the tail is of diagnostic value. These microfilariae do not occur in the peripheral blood but are found typically in the subcutaneous nodules near the parent worms, in the dermis, and in the tissues of the eye.



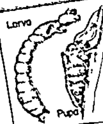




Figure VII 44. Epidemiology of onchocerciasis.



Figure VII 45. Onchocerciasis—microfilariae in skin. (Courtesy of Dr M. Martinez Baez, Mexico D F.)



Figure VII 46 Section through onchocercal nodule showing small abscesses and numerous adult worms Large worms are females small ones males

The vectors of onchocerciasis are species of black flies of the family
SIMULIIDAE These become infected as they suck blood and tissue juices
om the skin of an infected host Ingested microfilariae leave the food
eservoir of the fly and penetrate the thoracic muscles where develop
ment of the larvae takes place A period of at least six days during which
time two molts occur is required for development The infective larva
then travels to the labium of the fly at which time the insect becomes
infective

Epidemiology Man is the reservoir for the filarial worm *O vol*
vulus In Africa *S damnosum* and *S neavei* are the chief vectors of on
chocerciasis whereas in Guatemala Venezuela and Mexico *Eusimulium*
avidum (= *S metallicum*) *E ochraceum* and *E mooseri* (= *S calli*
dum) transmit the disease *S exiguum* *S veracruzanum* and *S hemato*
potum have been infected experimentally and should be added to the
potential vectors in Guatemala Most of the species of the SIMULIIDAE
transmitting onchocerciasis breed in the riffles of rapidly flowing streams
where the larvae and pupae may be found attached to submerged stones
logs or even vegetation A few species prefer the more slowly flowing
water of roadside ditches (Fig VII 44)

Buffalo gnats turkey gnats or black flies as these simuliids are called
are small "hump backed" flies 1 to 5 mm long Ordinarily they are out
door day biters but in Guatemala they will bite indoors even at night in
the presence of artificial light African species apparently do not enter
houses The bite is painless and the fly is not easily disturbed when it
has started feeding Transmission of the disease occurs only through the
female fly which feeds on an infected person

Pathology In some cases the adult worms provoke no tissue re
sponse in the human host More commonly however they cause a local
inflammatory reaction followed by fibrous encapsulation and the pro-
duction of subcutaneous nodules These tumors are distributed over re
gions of the body where there is convergence of the superficial lym
phatics Histologically they show a relatively low grade of inflammation
a leukocytic infiltration in which eosinophils are conspicuous and a
heavy deposition of collagen fibrils As a rule the nodules are solid
though infrequently where the adult parasites die and degenerate or
where secondary bacterial infections have occurred abscesses have re
sulted Usually microfilariae are abundant within the nodules They may
be found in the skin but not in the circulating blood (Figs VII 45
VII 46)

The incidence and the severity of the ocular pathologic changes in
onchocerciasis bear no relation to the anatomic situation of the nodules
the duration of the infection or the age of the individual Accumulatin
evidence indicates that the underlying mechanism is related to the d
velopment of sensitivity to antigenic substances of the parasite or
products of metabolism or disintegration

The essential pathologic process is a low grade chronic iritis and
docyclitis with occasional acute exacerbations which lead to synecl
distorted contracted eccentric pupils pigment deposits and corr
opacities Superficial punctate keratitis is so common as to be al

pathognomonic Dead microfilariae have been identified in these minute opacities and the latter have been observed to increase in number following treatment which kills the microfilariae Blindness results from pupillary occlusion corneal opacity or both

Clinical Characteristics The subcutaneous nodules are the most characteristic lesions of onchocerciasis However these onchocercomas are not always demonstrable In the Central American form of the disease the nodules are most numerous over the head and thorax in Africa they are predominantly on the trunk

In the typical case, following the bite of an infected fly, there is an incubation period of several months before nodules appear There is little if any systemic reaction The nodules grow slowly attaining full size in three or four years when they may reach a diameter of 2 to 3 cm There may be few on one individual and over a hundred on another Ordinarily they cause little inconvenience, although in the vicinity of joints they are often painful Inflammatory reactions may occur in and about certain nodules occasionally followed by abscess formation These may be due to secondary bacterial infection or to an allergic reaction Pruritus may be troublesome A facial complication observed in Guatemala "erysipelas de la costa" formerly considered to be bacterial in origin is almost certainly allergic since it is reproduced exactly in hypersensitive patients following treatment with Hetrazan

Ocular pathologic changes are the most serious feature of onchocerciasis The incidence of eye lesions has been reported as high as 30 per cent in certain groups in Central America and up to 85 per cent in Africa In Guatemala blindness occurs in about 6 per cent of patients with ocular lesions These complications usually do not appear until some years after the initial infection The early symptoms include conjunctivitis lacrimation and photophobia Serious involvement is indicated by circumcorneal congestion iritis and punctate keratitis of the cornea

Two complications of onchocerciasis often seen in Uganda and Kenya are hanging groin and hernia The hanging groin is a sac of atrophic skin containing sclerosed inguinal or femoral lymph glands This condition predisposes to hernia

Diagnosis Blood smears do not demonstrate the microfilariae of *O volvulus* An eosinophilia averaging about 35 per cent is frequently present

Diagnosis depends upon demonstration of the microfilariae in the skin *or nodules (Fig VII 47) Ordinarily they are not found in greatest num*bers over or adjacent to subcutaneous nodules In the Central American disease they are most consistently found in the skin of the scapular and neighboring areas and in the African form in the pelvic girdle and thigh regions

Skin biopsy, taking a thin section of superficial skin with a razor blade is the simplest and probably the easiest diagnostic technique The excised skin should be mounted in saline under a cover glass (Fig VII 47) A

[illegible] several closely approx[illegible]

[illegible]d preparing a smear of

[illegible]ematoxylin or Giemsa s



Figure VII 47 Unsheathed microfilaria of O volvulus in aspirate from skin. Caudal nuclei do not reach tip of tail.

stain Aspiration of a subcutaneous nodule and examination of the fluid will frequently reveal large numbers of microfilariae

When the eye is involved examination of the cornea under oblique illumination will frequently reveal minute superficial opacities—the superficial punctate keratitis which is almost pathognomonic of onchocerciasis

The prognosis is good unless ocular complications have appeared

Treatment. Whenever possible all tumors should be excised particularly in view of the danger of later ocular complications This is frequently impracticable however when large numbers of the nodules are present Such treatment is not always followed by disappearance of the microfilariae probably because other adult worms remain in the hosts tissues

Drug treatment of onchocerciasis must be undertaken with caution in the presence of ocular involvement since severe reactions may occur in

in) is an effective

muscle and joint

pains abdominal pain and nausea These should be treated symptomatically Hyperesthesia of the soles of the feet may be troublesome in some individuals Pruritus and subjective ocular reactions apparently allergic in nature may be controlled by antihistamine preparations Treatment should be discontinued if severe symptoms peripheral edema or evidence of renal damage occur Suramin is contraindicated in the presence of renal disease

Light weekly doses of Suramin should be administered intravenously dissolved in 10 ml of sterile distilled water For an adult the initial dose is 0.5 gram and the succeeding doses 1 gram

Suramin causes the death of adult worms and the slow disappearance of microfilariae Whenever possible large subcutaneous nodules should be excised since abscess formation may follow the death of the adult worms All of the ocular damage in onchocerciasis is not reversible but patients may recover a degree of vision after Suramin therapy

Diethylcarbamazine (Hetrazan) is of some value in the treatment of onchocerciasis Although it rapidly kills the microfilariae, severe allergic reactions are not uncommon in sensitized patients, and *in the presence of* ocular lesions severe damage to the eye may result Hetrazan has little or no effect upon the adult worm The limited effect of diethylcarbamazine (Hetrazan) on the adult forms of *Onchocerca volvulus* and the severe reactions which frequently follow administration of the drug to *persons with this infection constitute serious objections* to its use in mass

treatment with Hetrazan and Suramin is more inconvenient and not superior to Suramin alone

Prophylaxis. Satisfactory control measures directed against the breeding places of the vector are difficult and often impractical In Africa, aerial spraying of DDT and the introduction of DDT into larger streams and rivers has proved effective In Central America however, the vectors breed in much smaller, more rapidly flowing streams, and this renders effective control difficult There is no satisfactory personal prophylaxis other than avoidance of endemic areas Repellents are of doubtful value

Onchocerciasis has been shown to persist, with clinical manifestations and progressive ocular disease over a decade after elimination of transmission by blackfly control measures Therefore, effective control of onchocerciasis requires both the eradication of the vector and the treatment of all heavily infected cases

Loiasis

Synonyms. Calabar or fugitive swelling disease, eye worm disease of Africa

Definition. Loiasis *is due to the presence of the parasitic* filarial worm, *Loa loa*, in man, where it frequently causes calabar or fugitive swellings Tabanid flies, *Chrysops* spp, are the intermediate hosts and *vectors*

Distribution. Loiasis is a disease of tropical Africa where it is endemic along the Congo River watershed It is also prevalent on the coastal *plains and* delta regions of Sierra Leone as well as in Angola and the Cameroons

Etiology. *Morphology* The loa or eye-worm, *L loa* (Cobbold 1864) Castellani and Chalmers, 1913 produces loiasis or fugitive swellings as the adult migrates about the subcutaneous tissues of man

The male averages 30 to 34 mm long, the female ranges between 50 and 70 mm In both sexes the body is filiform, semitransparent and bluntly

tapered at both extremities The head is characterized by two lateral and four small semimedian papillae lying in the same transverse plane a little below the mouth The latter passes directly into a slender muscular esophagus The cuticula of these parasites is covered with small bosses except for a portion of either extremity of the male

The posterior end of the male is ventrally curved and possesses narrow lateral alae and eight pairs of perianal papillae (five anterior and three posterior) which are diagnostic The copulatory spicules are unequal in length and shape and the cloacal orifice is surrounded by a powerful sphincter

The broadly rounded posterior tip of the female carries a pair of terminal papillae The vulva opens about 2 5 mm from the anterior tip and passes into a posteriorly extending vagina which within 9 mm of its external aperature bifurcates to form twin uteri and other paired structures of the reproductive system The uterus contains developing em

[illegible]

per cent the anal pore 81 9 per cent The nuclei extend caudally to the tip of the gradually tapering tail In many respects the microfilariae of *L loa* resemble those of *W malayi* but may be distinguished by the arrangement of the caudal nuclei and the shorter cephalic space

Development The female liberates sheathed microfilariae which enter the blood stream and are diurnal in their periodicity The intermediate hosts for these worms are certain tabanid or "deer" flies belonging to the genus *Chrysops* The parasites undergo development in the thoracic muscles and fat body of the fly About ten days after infection the mature larvae about 2 mm in length migrate to the proboscis and remain infective for about a week After reaching man by the bite of the fly the parasites disappear into the subcutaneous tissues and mature slowly

Epidemiology Infection is acquired through the bite of infected tabanid flies of the species *Chrysops dimidiata C silacea C distinctipennis* and probably other members of this genus These flies are diurnal biters feeding primarily between dawn and 10 A M and again between 4 P M and dusk Only the females bite It has been noted that they prefer darker colors and are found more frequently in wooded areas They are believed to have a biting preference for the Negro however whites remaining in endemic areas for three to five years almost invariably become infected Such infections develop slowly and are known to persist for at least 15 years The finding of *Loa loa* in monkeys suggests the existence of a reservoir host

The incidence of loiasis in man varies with the prevalence of the native reservoir and dipterous intermediate hosts Loiasis has been reported from 15 per cent of the population along the Welle River in Rio Muni Central Africa other investigators have found infection rates of

90 per cent or more among the indigenous populations of the Belgian Congo

Pathology. Loiasis is a chronic disease frequently characterized by inflammatory processes and fugitive swellings of the subcutaneous tissues The adult worms migrate through the subcutaneous tissues at a maximum rate of about a centimeter per minute and have been removed from such locations as the back, axilla, groin breast penis scalp eyelids the anterior chamber of the eye and the bulbar conjunctiva Adult *L loa* are rarely encapsulated but usually migrate more or less continuously A marke'
present '
in the pe

Clinical Characteristics. The most outstanding clinical feature of the disease is the occurrence of the transient tumors known as fugitive or calabar swellings These are about the size of a small hens egg They appear suddenly, frequently preceded by pain, and in most cases persist for only two or three days They may cause inconvenience and disability, such as hampering the use of the hands and considerable irritability Fever, urticaria and pruritus may occur

A number of theories have been advanced in an attempt to explain the occurrence of calabar swellings It has been suggested that the swellings may be due to (1) the wanderings of the worm, (2) the liberation of large numbers of microfilariae by the female, (3) toxins secreted by the parasite, and (4) an allergic response on the part of the host A typical calabar swelling has been produced experimentally in a patient with loiasis by injecting antigen from the dog heartworm *Dirofilaria immitis*, thus supporting the concept of the allergic nature of such responses

External heat tends to bring the worm close to the surface of the body

Diagnosis Diagnostic findings in patients with loiasis include one or more of the following (1) calabar swellings (2) worm crossing the eye (3) edematous outline of the worm under the skin (4) microfilariae in films of the peripheral blood or in fluid aspirate of the calabar swellings A marked eosinophilia is usually present



Figure VII 48 Sheathed microfilaria of *Loa loa* in thick blood film. Caudal nuclei extend to tip of tail (From slide of Liverpool School of Tropical Medicine loaned by Puerto Rico School of Tropical Medicine From Bercovitz Z T Clinical Tropical Medicine Paul B Hoeber Inc 1944)

Microfilariae may be demonstrated in the usual thick smear or by concentration methods (see p 802) (Fig VII 48)

Differentiation between the microfilariae of *L loa* and the other sheathed species *Wuchereria bancrofti* and *W malayi* is necessary A detailed comparison is given on page 436 Diurnal periodicity, a tapering tail and the position of the caudal nuclei characterize *L loa* (Table VII 5)

Treatment. Loiasis responds well to treatment with diethylcarbamazine (Hetrazan) and both microfilariae and adult worms are killed However the first course of therapy is accompanied by allergic reactions in approximately 70 per cent of patients These occur particularly in the first three or four days and in highly sensitized patients may appear shortly after the first dose of the drug The most common reactions are the appearance of calabar swellings creeping sensations under the skin pruritus and fugitive papular erythematous eruptions Other symptoms include headache nausea and arthralgia more rarely there may be fever vomiting and diarrhea These reactions may be controlled by antihistaminics or corticosteroids and do not necessitate termination of treatment

The microfilariae are phagocytozed in the liver and rapidly disappear from the circulating blood The adult worms tend to appear under the skin where they are destroyed and small nodules are formed The initial course of Hetrazan therapy is commonly accompanied by a marked rise of the eosinophil count

The first course of Hetrazan should be as follows first day 0 1 gram second day 0 2 gram third day 0 3 gram fourth through tenth days 0 4 gram It is desirable to administer an antihistaminic drug prior to and for four days during the initial course of treatment with Hetrazan ACTH appears to be a useful adjunct in the treatment of loiasis with calabar swellings particularly during exacerbation of symptoms occurring during therapy with diethylcarbamazine since it reportedly provides prompt relief of swelling and pain

Mild symptoms of loiasis may reappear in the course of the second week following treatment these are due in part at least to the allergic mechanism A second course of Hetrazan should be given two or three weeks after completion of the first and it is probably desirable to give one or two additional courses to ensure eradication of the infection

Surgical removal of the migrating adult worms as formerly practiced is not recommended

Prophylaxis. Protection from bites of *Chrysops* in endemic areas will prevent the disease Oiling of the surface of the pools over which the flies skim will aid in their elimination as the spiracles or tracheal tubes become occluded by the oil thus causing suffocation. Repellents such as dimethylphthalate indalone or 6-2 2 are reported to be effective against these flies

Elimination of carriers by mass treatment of local population groups with Hetrazan will interrupt transmission of the disease The hazard of serious reactions in allergic individuals may limit or prevent mass therapy with Hetrazan

90 per cent or more among the indigenous populations of the Belgian Congo

Pathology. Loiasis is a chronic disease frequently characterized by inflammatory processes and fugitive swellings of the subcutaneous tissues The adult worms migrate through the subcutaneous tissues at a maximum rate of about a centimeter per minute and have been removed from such locations as the back, axilla, groin, breast, penis, scalp, eyelids the anterior chamber of the eye and the bulbar conjunctiva Adult *L loa* are rarely encapsulated but usually migrate more or less continuously A marked eosinophilia, sometimes as high as *50 to 70* per cent, may be present The microfilariae are diurnal and are found in greatest numbers in the peripheral blood during the middle of the day

Clinical Characteristics. The most outstanding clinical feature of the disease is the occurrence of the transient tumors known as fugitive or calabar swellings These are about the size of a small hen s egg They appear suddenly, frequently preceded by pain, and in most cases persist for only two or three days They may cause inconvenience and disability, such as hampering the use of the hands, and considerable irritability Fever, urticaria and pruritus may occur

A number of theories have been advanced in an attempt to explain the occurrence of calabar swellings It has been suggested that the swellings may be due to (1) the wanderings of the worm, (2) the liberation of large numbers of microfilariae by the female, (3) toxins secreted by the parasite, and (4) an allergic response on the part of the host A typical calabar swelling has been produced experimentally in a patient with loiasis by injecting antigen from the dog heartworm, *Dirofilaria immitis,* thus supporting the concept of the allergic nature of such responses

External heat tends to bring the worm close to the surface of the body

Diagnosis. Diagnostic findings in patients with loiasis include one or more of the following (1) calabar swellings, (2) worm crossing the eye, (3) edematous outline of the worm under the skin, (4) microfilariae in films of the peripheral blood or in fluid aspirate of the calabar swellings A marked eosinophilia is usually present



Figure VII 48 Sheathed microfilaria of *Loa loa* in thick blood film. Caudal nuclei extend to tip of tail. (From slide of Liverpool School of Tropical Medicine loaned by Puerto Rico School of Tropical Medicine From Bercovitz Z T *Clinical Tropical Medicine* Paul B Hoeber Inc 1944)

Microfilariae may be demonstrated in the usual thick smear or by concentration methods (see p 802) (Fig VII 48)

Differentiation between the microfilariae of *L loa* and the other sheathed species *Wuchereria bancrofti* and *W malayi* is necessary A detailed comparison is given on page 436 Diurnal periodicity a tapering tail and the position of the caudal nuclei characterize *L loa* (Table VII 5)

Treatment Loiasis responds well to treatment with diethylcarbamazine (Hetrazan) and both microfilariae and adult worms are killed However the first course of therapy is accompanied by allergic reactions in approximately 70 per cent of patients These occur particularly in the first three or four days and in highly sensitized patients may appear shortly after the first dose of the drug The most common reactions are the appearance of calabar swellings creeping sensations under the skin pruritus and fugitive papular erythematous eruptions Other symptoms include headache nausea and arthralgia more rarely there may be fever vomiting and diarrhea These reactions may be controlled by antihistaminics or corticosteroids and do not necessitate termination of treatment

The microfilariae are phagocytozed in the liver and rapidly disappear from the circulating blood The adult worms tend to appear under the skin where they are destroyed and small nodules are formed The initial course of Hetrazan therapy is commonly accompanied by a marked rise of the eosinophil count

The first course of Hetrazan should be as follows first day 0 1 gram second day 0 2 gram third day 0 3 gram fourth through tenth days 0 4 gram It is desirable to administer an antihistaminic drug prior to and for four days during the initial course of treatment with Hetrazan ACTH appears to be a useful adjunct in the treatment of loiasis with calabar swellings particularly during exacerbation of symptoms occurring during therapy with diethylcarbamazine since it reportedly provides prompt relief of swelling and pain

Mild symptoms of loiasis may reappear in the course of the second week following treatment these are due in part at least to the allergi mechanism A second course of Hetrazan should be given two or thre weeks after completion of the first and it is probably desirable to giv one or two additional courses to ensure eradication of the infection Surgical removal of the migrating adult worms as formerly practice is not recommended

Prophylaxis Protection from bites of *Chrysops* in endemic are will prevent the disease Oiling of the surface of the pools over wh the flies skim will aid in their elimination as the spiracles or trach tubes become occluded by the oil thus causing suffocation Repelle such as dimethylphthalate indalone or 6-2 2 are reported to be effec against these flies

Elimination of carriers by mass treatment of local population gr with Hetrazan will interrupt transmission of the disease The haza serious reactions in allergic individuals may limit or prevent mass th with Hetrazan

Filariasis Ozzardi

Synonyms Mansonelliasis ozzardi Ozzard s filariasis

Definition Filariasis ozzardi is due to the presence of *Mansonella ozzardi* in man The adults inhabit the body cavities, the nonperiodic microfilariae are found in the blood stream The intermediate host and vector is a midge of the genus *Culicoides*

Distribution *Mansonella ozzardi is confined exclusively to the* Western Hemisphere being native to parts of South America particularly the Guianas, Colombia Venezuela and northern Argentina It is also present in Panama Puerto Rico Yucatan and St Vincent and Dominica in the West Indies

Etiology. *Morphology* *Mansonella ozzardi* (Manson 1897) Faust 1929 is a nematode the adults of which are found in the mesenteries body cavities and visceral fat of man A complete male has not been described The female ranges between 65 and 81 mm in length and possesses an unarmed head a smooth cuticula and a pair of fleshy lappets or flaps at the caudal extremity The unsheathed microfilariae are 185 to 200 μ long and about 5 μ broad Both the cephalic and caudal extremities lack nuclei the nucleus free region comprising the anterior 2 2 to 2 5 per cent and the posterior 1 8 to 2 0 per cent of the worm Other measurements from the anterior tip are as follows the nerve ring 21 9 to 22 2 per cent excretory pore and excretory cell 30 9 to 31 5 and 35 per cent, respectively, the G_1 cell 67 9 to 69 3 per cent the G_4 cell just *in front of the anal pore at 79 4 per cent The outstanding diagnostic* characteristics are the lack of a sheath and the absence of nuclei in the posterior tip of the tail (see Table VII 5 p 436)

Development The unsheathed microfilariae are nonperiodic The larvae require five to seven days for development in the vector *Culicoides furens*

It appears probable that the *Microfilaria tucumana* of Argentina is identical with the microfilaria of *M ozzardi*

Epidemiology Even though the epidemiology of Ozzard s filariasis has not been adequately studied it has been demonstrated that transmission *occurs through the bite of an infected Culicoides furens C paraensis* appears to be another vector

The prevalence of this infection is not definitely known for most areas In endemic areas of the Argentine about 30 per cent of the population are believed to be infected

Pathology and Clinical Characteristics *The adult worms apparently* produce few if any pathologic changes or symptoms An occasional hydrocele or enlarged lymph node has, however been attributed to *M ozzardi* infections

Diagnosis This is based upon the recovery and the identification of the unsheathed *microfilariae from the peripheral blood* The pointed tail and absence of nuclei extending to the posterior tip are important diagnostic characteristics (see Table VII 5 p 436 for additional details) (Fig VII 49)



Figure VII 43 Unsheathed microfilaria of *M ozzardi* in thick blood films (Courtesy of F W O Connor from Bercovitz Z T Clinical Tropical Medicine Paul B Hoeber Inc 1944)

Treatment. None recommended Diethylcarbamazine is not effective against *M ozzardi*

Prophylaxis. No effective control measures are known, other than the use of repellents against midges These insects are so small that screening will not exclude them

Acanthocheilonemiasis

Synonyms Dipetalonemiasis, *Acanthocheilonema perstans* infection

Definition Acanthocheilonemiasis is due to the presence of *Acanthocheilonema perstans* in man The adults inhabit the peritoneal cavity the pleural cavity, pericardium mesenteries or retroperitoneal tissues the nonperiodic microfilariae are found in the blood stream The vectors are various species of *Culicoides*

Distribution. *Acanthocheilonema perstans* is common in the tropical regions of South America Africa and New Guinea In the Western Hemisphere it has been reported from British and Dutch Guiana, Venezuela the lower Amazon Valley, northern Argentina Trinidad and [illegible]

are often found in persons infected with *Wuchereria bancrofti*

Etiology. *Morphology* Adult *Acanthocheilonema perstans* (Manson 1891) Railliet, Henry and Langeron 1912 [= *Dipetalonema perstans* (Manson, 1891) Yorke and Maplestone, 1926] are elongated cylindrical, creamy white FILARIOIDEA with a smooth cuticle The anterior tip is unarmed and bluntly rounded although a shield possessing two large lateral papillae and two pairs of submedian papillae is present The

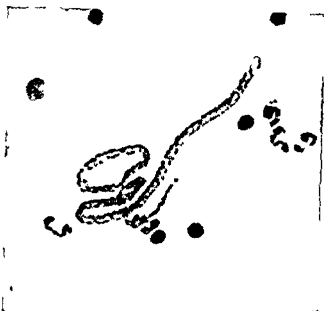


Figure VII 50 Unsheathed microfilaria of *A perstans* in thick blood film (hematoxylin stained) Note caudal nuclei extending to tip of tail and other morphologic characteristics (What appears to be a sheath is merely a halo)

caudal extremity is somewhat curved ventrally in both males and females and is bifurcated to form a pair of triangular nonmuscular flaps The female is 70 to 80 mm long the male averages about 45 mm The latter possesses four pairs of preanal papillae and one postanal pair with unequal rodlike copulatory spicules

Development The female produces unsheathed microfilariae measuring about 200 by 4 5 μ These enter the blood stream and are nonperiodic The intermediate hosts of this parasite include several species of *Culicoides* Development occurs in the midge which then transmits the infection when it next feeds allowing the infective stage to reach the skin of man

Epidemiology In Africa *C austeni* and perhaps *C grahami* serve as the vectors for this disease The vectors in other areas are unknown

The incidence of parasitism in man varies markedly The infection rates in northern Argentina range between 39 1 and 50 6 per cent In some areas of Africa such as Uganda the parasite has been found in about 90 per cent of the population and in the heavily wooded portion of the Cameroons the infection rate is more than 92 per cent As noted above the parasite is endemic in the Congo River basin and often appears concomitantly with *W bancrofti* in Africa and with *M ozzardi* in South America

Pathology and Clinical Characteristics The consensus of opinion is that *A perstans* is nonpathogenic However vertigo aching limbs pe- ... pain enlargement of spleen and ... of lower limbs and scrotum and ... ed to this filarial infection

Diagnosis. The detection and identification of the unsheathed microfilariae of *A perstans* in the peripheral blood are diagnostic These may be differentiated from the microfilariae of *M ozzardi* by the position of the caudal nuclei which, in the case of *A perstans,* extend into the posterior tip of the blunt tail but stop short thereof in the case of *M ozzardi* (Fig VII 50)

Treatment. None recommended Treatment with Hetrazan by mouth even in large doses fails to achieve a permanent cure

Prophylaxis. At present it does not seem feasible to control the breeding of *Culicoides* Ordinary screening does not exclude these midges Avoidance of endemic areas and the use of repellents are the only available prophylactic measures

48

Tissue-Inhabiting Nematodes: The Dracunculoidea

The DRACUNCULOIDEA are tissue inhabiting nematodes of which but a single representative, *Dracunculus medinensis,* infects man The adults may be distinguished from members of the FILARIOIDEA by their great size and their characteristic larvae, which are 500 μ or more long Copepods (minute crustacea) serve as intermediate hosts

Dracunculiasis

Synonyms. Dracontiasis, dracunculosis, medina, serpent, dragon or guinea worm infection

Definition. *Dracunculiasis is due to the presence of the guinea* worm, *Dracunculus medinensis,* in the deep connective and subcutaneous tissues of man Superficial lesions are formed through which the larvae are discharged

Distribution. The medina or guinea worm produces a disease which has been recognized in man for many centuries It is highly endemic in a number of regions in tropical Africa and over large areas of India

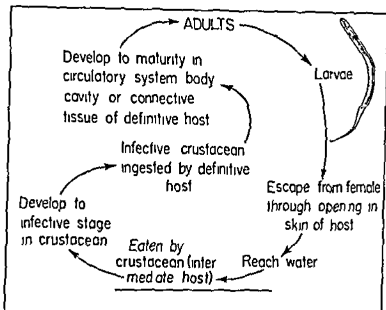


Figure VII.51 Nematode cycle—guinea worm type

Dracunculiasis occurs also in Arabia (especially along the Red Sea) Iran Afghanistan and Russian Turkestan The endemic centers in Africa lie between the equator and the Tropic of Cancer where they are scattered from Mauritania to Gabun especially in Mauritania Senegal Upper Volta Ivory and Gold Coasts Northern Territories Togo Dahomey Nigeria and the Cameroons Endemic centers extend east to Lake Chad *and to the southern parts of the Sudan and into Uganda It is also found* in the Nile Valley and in Iraq

The western half of India constitutes the next most important endemic center there is little infection east of Delhi and the central provinces Dracontiasis also occurs in limited areas of New Guinea some of the islands of the West Indies and in the Guianas

Guinea worms morphologically similar to those infecting man have been reported from monkeys baboons dogs leopards polecats cattle and horses from the Old World and possibly an identical species from *foxes mink and raccoons in North America However many* authorities are inclined to consider infections of the latter hosts as due to *D insignis*

Etiology *Morphology* *Dracunculus medinensis* (Linnaeus 1758 Gallandant 1773) is an elongate cylindrical threadlike worm Males of the species are rare They range in size from 12 to 40 mm The than the male averaging

and *she migrates* to the ... lower extremities As she approaches

uterus of the parasite prolapses through its body wall, ruptures, and liberates large numbers of larvae These larvae are 500 to 750 μ in length and have a maximum diameter of 15 to 25 μ Their anterior extremity is bluntly rounded, the caudal extremity is long and attenuated In order that the life cycle of these parasites be completed the larvae must be ingested by one of several species of copepods (Fig VII 51) Here they undergo a developmental period averaging ten to 12 days, after which time the copepods become infective Following ingestion of the intermediate host by man, the parasites probably mate, and the female migrates through the tissues After eight months to a year, the fertilized female approaches the skin to liberate her young thus completing the cycle

Epidemiology. Human infection results from drinking water containing infected copepods Many species of *Cyclops* serve as intermediate hosts In endemic areas, open wells and step wells provide a source of infected copepods Lesions in man occur most frequently on the appendages and larvae are released when an infected person wades in sources of drinking water In some parts of India religious ablutions include rinsing the mouth and this custom facilitates infection

Pathology. After an incubation period of eight to 12 months the female parasite approaches the skin and in 85 to 90 per cent of the cases migrates to some portion of the lower extremities Here a reddish papular lesion appears it has a domelike vesicular center, the margin of which gradually becomes indurated (Fig VII.52) The entire lesion may be 2 mm to 7 cm in diameter the size depends upon the amount of ex



Figure VII 52 Dracontiasis Track of part of the worm which became visible in skin following the appearance of the vesicle Note that the blister is now crusted that there is discoloration of the surrounding skin.



Figure VII 53 *Dracunculus medinensis partially extracted* (Courtesy of Dr J M Hulsey Jr through Dr Hardy A Kemp V A Hospital, Portland Oregon)

udate underneath the blister and the time elapsing before the blister ruptures Usually not more than 24 to 48 hours elapse between the first symptoms and the bursting of the lesion In many instances patients do not present themselves for treatment until after the blister has ruptured as a result secondary infection occurs in nearly half the cases An eosinophilia up to 15 per cent has been recorded in some infected individuals (Fig VII 53)

Clinical Characteristics The infection is asymptomatic during the entire incubation period of approximately eight to 12 months A few hours before the appearance of the worm beneath the skin there are pronounced symptomatic prodromes These consist essentially of erythema generalized urticaria severe pruritus giddiness asthmalike symptoms severe dyspnea and sometimes vomiting and diarrhea It is believed that these are reactions associated with toxic secretions of the parasite As the anterior extremity of the worm reaches the skin intense itching or burning sensations are frequently experienced

Diagnosis Diagnosis cannot be made until the cutaneous lesion has developed or until the adult worm presents itself immediately below the surface of the skin Although intradermal tests may be performed they are seldom needed as a diagnostic aid Partially or completely calcified worms may be detected by x ray The larvae are found only in the washings of the ulcers through which the gravid females discharge their young

Treatment Hetrazan in large doses taken orally is lethal to the adult worms Immature forms of the parasite are destroyed when this drug is employed prophylactically

Satisfactory results are reported in the treatment of dracunculiasis when olive oil emulsions of phenothiazine are injected The worms are killed and absorbed To prepare the emulsion, triturate 2 grams of phenothiazine with 0 35 gram of lanolin in a sterile mortar and with 15 ml of sterilized olive oil (heated to 150° C for one hour) The addition of 5 ml of sterile water produces an emulsion Add another 20 ml of sterile olive oil, pour the emulsion into a sterilized 2 oz bottle, seal and autoclave at 115° C for 30 minutes The appropriate areas should be injected with a local anesthetic prior to use of the anthelmintic Shake the phenothiazine emulsion vigorously Inject 20 ml of the emulsion intramuscularly as near the buried worm as possible and 10 ml on each side Massage the injection sites firmly for five minutes

The time honored custom of "forcing parturition by the use of wet pads and then rolling the worm on a stick is not recommended However, this method will doubtless continue to be used in some remote areas

Prophylaxis. As infection comes from swallowing water containing infected copepods control centers around the destruction of the copepods and the covering of wells so that the water may not be contaminated by infected persons This may be accomplished as follows (1) Eliminate the so called step wells (2) Construct a cement curb around wells (3) Treat the water with quicklime in dilution of 1 1000 When used in a strength of one ml per liter (80 per cent CaO) this water is potable in two days and remains free of copepods for two weeks (4) Copper sulfate in combination with Perchlon is also effective (5) Introduce DDT, 10 parts per million in pond water for household use, but not for drinking (6) Biologic methods of control may be introduced Almost any small plankton feeding minnow will keep down the copepods In Indian step wells *Barbus puckelli* has been found to be a voracious feeder on copepods and their larvae

49

Other Tissue-Inhabiting Nematodes

Trichinosis

Synonyms Trichiniasis, trichinelliasis

Definition. Trichinosis is a disease caused by the parasite, *Trichinella spiralis* It runs an acute and rapid course and is characterized by fever, gastrointestinal symptoms myalgia and eosinophilia

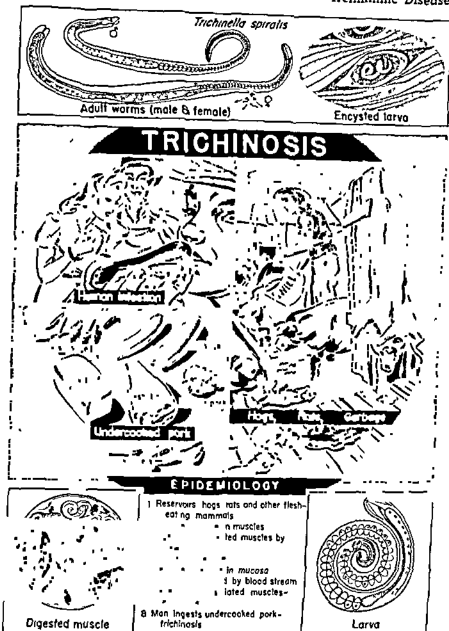


Figure VII 58. Epidemiology of trichinosis

insufficiently-cooked pork products containing striated muscle A sampling of a large proportion of the population reveals that nearly 18 per ... of the people in the United States are infected An infection by a

is examined

Occasional outbreaks have also been traced to such unusual sources as jerked infected bear meat

Pathology Trichinosis causes localized inflammation and necrosis in muscle tissue The penetration of striated muscle fibers by the larvae of *T spiralis* causes the destruction both of the fibers in which the larvae lie and of the adjacent ones The parasites grow rapidly and even after encystment distention of the cysts occurs causing further damage to adjacent tissues In severe infections the myocardium may be extensively damaged presenting cellular infiltration and necrosis and fragmentation of the muscle fibers Encystment however does not occur in cardiac muscle It is believed that the destruction and absorption of host tissue and of many of the larvae causes the generalized toxemia A high eosinophilia sometimes reaching 70 per cent is typical of this disease In fatal cases death usually intervening four to eight weeks after the infection is due to toxemia secondary pneumonia myocardial failure or trichinous encephalitis (Figs VII 57 VII.58)

Clinical Characteristics The clinical picture may be divided roughly into the stages of intestinal invasion muscle penetration and tissue repair (encystment) Twenty four hours following the ingestion of viable larvae signs of gastrointestinal disturbance in the form of nausea vomiting diarrhea and abdominal pain may become evident In about a week the females begin to larviposit and the stage of muscle penetration commences This period is characterized by periorbital edema which usually occurs between the 12th and 14th day and irregular but persistent fever lasting one or two weeks and reaching a maximum of 104° to 105° F Myositis and "rheumatic pains" are especially noticeable at this time In severe infections a generalized scarlatiniform rash may occur During this acute phase differential blood counts reveal a marked eosinophilia The last stage is characterized by neurotoxic

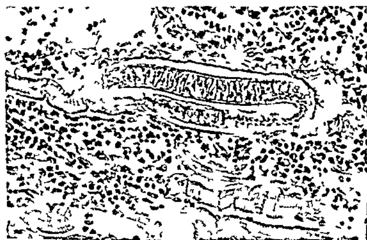


Figure VII 57 Early stage of encystment of larva of *T spiralis* in man, showing degeneration of muscle fiber and surrounding myositis

morphology of this species is essentially similar to that of *A duodenale* *Ancylostoma braziliense* has two pairs of teeth, a small, curved, inner pair and a larger, outer pair, making the buccal capsule diagnostic of the species The bursa of the male is smaller than that of other hookworms and is likewise diagnostic, it is almost as broad as it is long and is supported by short stubby rays The eggs cannot be distinguished readily from those of *A duodenale.*

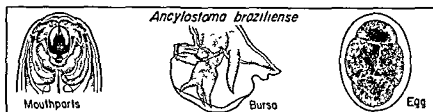


Figure VII 59 Epidemiology of creeping eruption.

Development The females produce about 4000 eggs a day The extrahuman developmental cycle parallels that of the other hookworms The filariform larvae however usually remain localized in the skin of man and do not undergo further development

Epidemiology. Wild and domestic members of the dog and cat families constitute the normal and reservoir hosts of *A braziliense* The eggs are passed in the stools and contaminate the soil where, under adequate conditions of temperature and humidity infective filariform larvae develop (Fig VII 59) These coming in contact with the skin of man readily penetrate and produce "creeping eruption" Sandy areas of the southeastern states constitute the chief endemic foci in this country Beaches childrens sand piles and areas where dogs and cats defecate are common sources of infection Less extensive lesions of creeping eruption have been reported for the European dog hookworm *Uncinaria stenocephala* and experimentally by the dog hookworm *Ancylostoma caninum*

Pathology The larvae after penetrating the epidermis produce serpiginous tunnels in the stratum germinativum of the skin progressing at a rate of several millimeters or a few centimeters each day The course of the tunnels is marked by erythema induration and at times overlying vesiculation Histologic examination reveals local eosinophilic and round cell infiltration The larvae may remain active in the skin for variable periods up to several months In some human infections larvae reach the lungs and may cause transient pulmonary infiltration

Clinical Characteristics A reddish papule accompanied by pruritus occurs at the site of invasion within a few hours after the larvae have penetrated the skin Within two or three days the parasites begin to migrate producing an erythematous serpiginous linear and elevated tunnel This migration is accompanied by an intense pruritus The unoccupied portion of the tunnel soon dries and becomes crusted Scratching of these lesions frequently leads to secondary infection The infected person may suffer intolerably the local symptoms producing insomnia anorexia and even loss of weight (Fig VII 60) Loefflers syndrome—eosinophilia cough and x ray evidence of transient pulmonary infiltrations—occasionally occurs

Diagnosis *Ancylostoma braziliense* infection may be diagnosed most readily on the basis of the characteristic serpiginous lesions and a history of exposure in a typical "creeping eruption environment A differential diagnosis between "creeping eruption and other types of dermatitis caused by metazoan parasites is sometimes difficult Considerable confusion is possible but a careful analysis and reference to the accompanying table should prove helpful (Table VII 8)

Treatment. Permanent relief is accomplished by freezing the area just ahead of the lesion with ethyl chloride spray or carbon dioxide snow This is a commonly employed therapeutic measure but at best is unsatisfactory especially if numerous lesions are present

The oral administration of promethazine hydrochloride (Phenergan) reportedly provides effective therapy Children up to six years of age

Table VII.8. Differential Diagnostic Chart of Cutaneous Lesions Produced by Some Metazoan Parasites

PARASITE	CHARACTER OF THE LESIONS
Necator americanus "American" hookworm	Penetration of larvae is followed by itching, burning, erythema and edema. Later a papule appears, followed frequently by a vesicle. If secondary infection does not occur, the dermatitis disappears spontaneously in two weeks. This is known commonly as "*ground itch*," or "*dew itch*."
Ancylostoma duodenale "Old World" hookworm	May cause "ground itch" as above, but not invariably, some cases being asymptomatic
Ancylostoma braziliense Dog and cat hookworm	The commonest type of "creeping eruption." Lesions serpiginous, extending sinuously through the stratum germinativum from several mm. to several cm. daily. Erythema, *or even purpura, make the "burrows" superficially* visible, in addition to elevation of the skin over the tunnels. The chief symptom is intense itching. The worms live for weeks or months. Secondary infection may complicate the disease. Pulmonary involvement develops occasionally
Ancylostoma caninum The dog hookworm	Penetration is followed by itchy papules, occasionally with linear extension by "burrowing." Symptoms usually disappear in two weeks
Uncinaria stenocephala European dog hookworm	This nematode, the European dog hookworm, produces a condition practically identical with the "creeping eruption" of *Ancylostoma braziliense* but is of shorter duration
Strongyloides stercoralis The strongylid threadworm	On rare occasions infections produce a pruritus at the site of entry within an hour, characterized by an erythematous macule. Generalized urticaria occurs occasionally, serpiginous lesions are seen only rarely
Gnathostoma spinigerum Gnathostomes	This nematode forms boils, abscesses, or deep burrows. *Infiltration by WBC, especially eosinophils, is seen* histologically
Dermatobia hominis The tropical warble fly	Deeply penetrating, with an open "breathing hole" in skin. No migration. Elevated red itchy painful boil or "bot" or "warble." Duration about six weeks (see p. 750)
Gasterophilus sp. Horse bot fly	Penetrates to stratum germinativum, then burrows parallel to skin surface, migrating slowly for several months. Looks more like true "creeping eruption" of *A. braziliense than any other similar lesion* and is called "larva migrans" (see page 749)
Hypoderma sp. Cattle warble fly	*Deeply penetrating to subcutaneous tissue. Slow migra*tion occurs during the course of a month. Quite painful. Little itching (see page 752). More serious than *Gasterophilus*
Schistosoma, species for which man is an abnormal or unfavorable host. Blood flukes	Known as schistosome dermatitis or swimmers' itch. Urticarial wheals immediately after penetration of cercariae. Several hours later itching and edema, followed by papules and pustules. Symptoms begin to subside after three days (see page 513)



Figure VII 60 Creeping eruption caused by the larvae of *Ancylostoma braziliense* (Courtesy of Dermatology Division University of Miami Medical School)

receive 50 mgm at bedtime older children 75 to 100 mgm and adults 150 mgm or more The above doses are repeated on three successive nights Occasionally an additional course is given in the same or increased dosage The hyperexcitability that patients may occasionally experience after the first dose may be controlled by an immediate additional dose of the same amount

Chloroquine diphosphate (Aralen) has sometimes given favorable therapeutic results for this nematodiasis Aralen is administered 0 25 to 0 5 gram twice daily for ten days to adults and 0 125 gram twice daily to children for the same period Antipruritic shake lotions and oral Benadryl are used when patients complain of severe pruritus

Hetrazan Fuadin and Stibanose the latter supplemented by topical application of ethyl acetate collodion have given variable results In severe infections elevation of the part and application of wet dressings of a saturated solution of magnesium sulfate will give partial and temporary relief

Prophylaxis Avoid contact with sandy soil which dogs and cats may leave polluted with feces Sand boxes and the like should be protected from dogs and especially cats which may select these as defecation sites Periodic deworming of these domestic animals should be helpful in reducing infection

Gnathostomiasis

Synonyms *Gnathostoma spinigerum* infection larva migrans or

in infection caused primarily by *dolorosi* and *G nipponicum* also

have been incriminated in Japan The worm may localize in the internal *organs but also may occur in the peripheral tissues in nodules or in* subcutaneous tunnels in which the worms migrate (hence "larva mi *grans" or "creeping eruption")*. *Adult* parasites are usually found in wild or domestic cats and more rarely in dogs, hogs or mink

Distribution. *Gnathostomiasis is* known from Israel, India, Java, Malaya, Thailand, China and Japan In certain areas of Thailand it is highly endemic Since World War II, *it has become an important medical* problem in Japan

Etiology. *Morphology* The adult nematode, *Gnathostoma spinigerum* (Owen, 1836), *is stout, reddish in color and possesses a globose* cephalic bulb or head which is separated from the body proper by a slight constriction and is armed by four to eight transverse rows of recurved spines The anterior half of the body is spinose also Males and females range respectively from 11 to 25 mm and 25 to 54 mm in length The mature female produces ovoid, unsegmented eggs with a greenish tinged, irregularly pitted shell that is marked by a transparent plug *at one end, the eggs are 63 to 70 μ long by 37 to 41 μ broad*

Development The adult worms lie coiled in tumors along the alimentary canal of cats, dogs and other reservoir hosts Eggs reach the lumen *of the* intestine from these lesions and are passed in the feces, where they become embryonated They hatch upon reaching water, *releasing a cylindrical,* [illegible] *ich, if ingested* by a copepod (*Cyclo*[illegible] the infective copepod is eaten by a [illegible] stage larva is produced which becomes encapsulated in the flesh of the host Upon ingestion by the definitive host, the parasite usually becomes localized in the stomach wall where it matures after about seven months

Epidemiology. Man becomes infected with S *spinigerum* through the ingestion of improperly cooked fish, frogs, birds and snakes containing encapsulated larvae It appears doubtful that man becomes infected by swallowing infected copepods in water

Pathology. Obviously man is an abnormal host Only immature worms have been encountered When the parasites are situated superficially, abscesses or cutaneous nodules may be produced Subcutaneous *tunnels may be formed by the migrating nematodes Ocular involvement* occurs rarely

Clinical Characteristics. Visceral invasion probably is common *but often goes unrecognized* Creeping eruption is considered to be a less frequent but more obvious form of the infection The worms, which are situated superficially, usually are encountered between the stratum germinativum and the corium of the skin, producing local inflammation, edema, eosinophilia and leukocytosis Other symptoms depend upon the location of the parasites Infection may persist for long periods—up to 17 years

Diagnosis. Residence in an endemic area is suggestive, but definitive diagnosis *depends upon recovery* and identification of the parasite Skin testing provides a reliable means of diagnosis The nonmigrating *type of infection* must be differentiated from abscesses of bacterial origin,

the superficial migrating form must be distinguished from cutaneous myiasis (p 740) or the migrations of larval hookworms especially *Ancylostoma braziliense* (p 481)

Treatment. Hetrazan has some therapeutic value in cutaneous gnathostomiasis The recommended dosage is 0 5 to 0 7 mgm per kilo gram of body weight three times daily after meals for five to seven days

Prophylaxis Since man acquires this helminthiasis by ingestion of infected fish frogs birds or snakes adequate cooking of the flesh of these animals is recommended Immersion of fish in vinegar for five and one half hours has also been found to be an effective measure

Visceral Larva Migrans

Synonyms Human toxocariasis nonpatent nematodiasis

Definition Visceral larva migrans denotes prolonged migration of larvae of animal nematodes in human tissues other than the skin The syndrome in persons who react significantly to the presence of the larvae is characterized by persistent hypereosinophilia hepatomegaly and frequently by pneumonitis Larvae of dog and cat ascarids and of other animal nematodes may produce this entity The infection occurs predominantly in children

Distribution Most of the cases have been reported from the United States The infection probably occurs widely throughout the world

Etiology *Toxocara canis* (Werner 1782) a common ascarid of dogs probably is the most important etiologic agent Opportunity for infection of children with eggs of this animal nematode in soil is favored by the close association of dogs with humans and the animals habit of promiscuous defecation *T cati* (Schrank 1788) an ascarid of cats is probably of somewhat lesser epidemiologic significance Some of the other nematodes presently known to be involved in the larva migrans type of infection in man are *Capillaria hepatica* (Bancroft 1893) a parasite of rodents certain species of gnathostomes and other spiruroids species of hookworm including *Ancylostoma braziliense* (de Faria 1910) and *A caninum* (Ercolani 1859) and one or more species of animal filariae of the genus *Dirofilaria*

Epidemiology *Toxocara canis* and *T cati* eggs deposited in yards and scattered by rain may embryonate in soil under favorable environmental conditions Owing to the habit of toddler age children of eating dirt eggs of the ascarids may be ingested The mode of infection is similar to that of human ascariasis and trichuriasis except that the infective eggs are of animal origin Adults may acquire the infection from soiled hands and food or water contaminated with *Toxocara* eggs The larvae emerge from the eggs in the intestine of the human host penetrate the bowel wall and by direct migration or through the circulation

reach the various organs of the body The extensive somatic migration may continue for an undetermined period probably many months It is followed by encapsulation of the larvae which may persist without morphologic change for more than a year *Toxocara* infections rarely reach maturity in the human intestine since man is not a natural host

Pathology Scattered gray nodules up to 0 7 cm in diameter may be seen in the liver lungs and other organs at autopsy A granulomatous eosinophilic and neutrophilic inflammatory reaction surrounds the worms and their tracts Typically the lesion is an eosinophilic granuloma Charcot Leyden crystals have been observed in the allergic granulomata The continuous active movements of the larvae may be responsible for considerable tissue destruction Meticulous search of many sections usually is necessary to find larvae in biopsy material Later they are encapsulated by connective tissue Larvae are most abundant in the liver lungs and brain but to a lesser extent may invade almost all organs of the body Irreversible changes in the central nervous system occasionally occur The bone marrow shows an eosinophilic hyperplasia

A nematode endophthalmitis represents another form of visceral larva migrans The most characteristic lesion is an eosinophilic abscess that is frequently located on the underside of the retina in the retinal folds *and in the vitreous membrane*

Clinical Characteristics Many infections are subclinical and the only salient finding is a moderate or high sustained eosinophilia In *symptomatic infections a syndrome consisting of hypereosinophilia* hepatomegaly hyperglobulinemia and frequently a patchy pneumonitis is commonly seen Intermittent fever leukocytosis primarily due to the *increase in eosinophils malaise pallor anorexia* failure to gain weight muscle and joint pains abdominal pain nausea vomiting and neurologic disturbances with convulsions and petit mal attacks may occur in some cases An impetiginous pruritic skin rash sometimes appears on the trunk and extremities

The infection usually runs a chronic benign course as long as 18 months and is self limited in the absence of reinfection Deaths attributed to this infection have been few The severity of the infection varies ... llergic
state ... y
cases ... al
eosinophilia Weingarten s disease Frimmodt Moller s syndrome eosinophilic pseudoleukemia tropical eosinophilia and Loeffler s syndrome

A nematode endophthalmitis clinically resembling retinoblastoma may be caused by larvae migrating to the orbit This entity has been most frequently observed in children

Diagnosis *A high and persistent eosinophilia in a child* should arouse suspicion of visceral larva migrans The diagnosis is made primarily on clinical grounds A history of eating dirt or playing on ground frequented by *dogs or cats* the presence of these pets at home and previous or present infection with intestinal helminths which could have been acquired simultaneously help to support a clinical diagnosis Differential and total leukocyte counts may reveal an eosinophilia of 90 to

80 per cent and 15 000 to 80 000 white blood cells Intradermal tests are not sufficiently specific Experimental studies indicate that the hemag glutination or bentonite flocculation tests may be specific enough to dis tinguish larval *Toxocara* infections (p 836)

Since the parasite does not complete its life cycle in man the patient s stools do not contain *Toxocara* eggs

Liver biopsy is not recommended However the diagnosis of second stage rhabditoid *Toxocara* larvae in tissue sections can be made from one good cross section at the midgut level *T canis* ranges in maximum diameter from 14 to 20 μ and *T cati* 12 to 16 μ Both *Toxocara* species have average lengths of 320 μ Second stage larvae of *Ascaris lumbri coides* resemble those of *Toxocara* but the third stage larvae are much larger and measure about 600 μ in length and 24 to 26 μ in diameter

Differential diagnosis includes pneumonia miliary tuberculosis asthma whooping cough Loeffler s syndrome tropical eosinophilia and intestinal helminthiases Strongyloidiasis trichinosis and other helminthic infections in which there may be a marked increase in eosinophils may need to be excluded Larval *A lumbricoides* occasionally may produce a similar syndrome in some children Histologically the lesions may simulate peri arteritis nodosa and sarcoidosis and the blood picture may suggest eosinophilic leukemia In some instances retinoblastoma and endophthal mitis of other etiology must be considered Ocular lesions of visceral larva migrans have been confused with pseudoglioma Coat s disease and endophthalmitis of unknown origin Specific diagnosis of nematode en dophthalmitis is made only after enucleation of the organ

Treatment There is no effective therapeutic Cortisone may be used in selected cases to ameliorate the symptoms and reduce the eosino phil count Usually no specific treatment is necessary The prognosis ordinarily is good if the source of infection is removed Measures to prevent superinfection are extremely important in management of pa tients with this infection

Prophylaxis Dogs and cats should be dewormed at monthly in tervals In some instances it may be desirable to dispense with these pets When practicable play yards should be protected by fences to exclude pets and stray dogs Paved areas and lawns are preferable to open soil and sand boxes as play sites Top soil may be turned under to place the eggs out of reach of children Instruction of children and supervision of their hygienic and play habits to reduce the ingestion of soil and the placing of contaminated hands in the mouth are of great importance

50

The Schistosomes

Revised by Henry E Meleney

Introduction. The schistosomes of man commonly known as blood flukes, are the most important human trematodes It has been estimated that over 100 million people are infected and the number may be increasing There are three species which infect man—*Schistosoma haematobium*, *S mansoni* and *S japonicum*—each producing its characteristic disease Other species, such as *Schistosoma bovis*, normally a parasite of cattle, have been reported as occasional human parasites hence these will be mentioned only briefly The generic name *Bilharzia* after Bilharz the discoverer of the worms in Egypt in 1852, is often used for *S haematobium* and *S mansoni* in Europe and Africa

Morphology. These parasites differ from other trematodes of man in that they are dioecious (exist as males and females) (cf p 516) They range in length between 6 5 and 26 mm, the females are longer and more slender than the males They are cylindrical and possess an oral and a ventral sucker or acetabulum the latter being situated near the anterior end The most characteristic feature of the males is their ventrally infolded margins beginning behind the acetabulum and forming a groove or *gynecophoral canal* in which the more slender female is carried during most of its life The alimentary canal passes from the oral cavity into an *esophagus* which divides just anterior to the acetabulum forming two *intestinal canals* which fuse near the center of the worm to form a single serpentine trunk extending to a blind terminus near the posterior end of the worm The gut frequently appears reddish black owing to the presence of ingested blood The male reproductive system consists of four to nine *testes* located dorsally just posterior to the acetabulum and connected by tubules to the seminal vesicle and genital pore on the ventral surface The female system consists of a single *ovary* situated just anterior to the fusion of the two branches of the intestine a *seminal receptacle* adjacent to it, an *oviduct* leading forward to an *ootype* and *shell gland*, yolk glands (*vitellaria*) occupying the posterior half of the body with ducts leading to the ootype, and a *uterus* passing [illegible]

head into these vessels The uterus may contain only one egg at a time (*S mansoni*) or as many as 300 (*S japonicum*)

Table VII.9. Characteristics of Schistosome Eggs

SPECIES	LENGTH (MICRONS)	BREADTH (MICRONS)	DIAGNOSTIC FEATURES
S haematobium	112 170 av 150	40–70 av 60	Terminal spine
S mansoni	114–175 av 150	45–70 av 60	Lateral spine
S japonicum	70–100 av 89	50–70 av 66	Small spine or knob which often is not seen

Schistosome Eggs. These differ from the eggs of all other trematodes in the absence of an operculum or lid and the presence of a spine or knob on the shell (see Fig VII 78 p 518) In addition schistosome eggs contain a fully developed *miracidium* when they leave the host Table VII 9 summarizes some of the more important characteristics

The Generalized Cycle of the Schistosomes

Oviposition. The female worm matures following fertilization by the male after which the male carries the female in its gynecophoral canal The male transports the female against the current of the portal blood stream by means of its suckers into the smaller radicles of the mesenteric veins In the case of *S haematobium* the worms migrate through the hemorrhoidal plexus into the systemic veins of the pelvis especially those of the urinary bladder Here the female may partially or entirely leave the gynecophoral canal of the male in order to migrate further into the venule The eggs are deposited in a beadlike row, often in the capillaries of the mucosa after which the female retreats into a larger venule allowing the smaller vessels to contract about the eggs The embryo within the egg rapidly matures and apparently secretes a substance which seeps through the porous egg shell and causes necrosis of the vessel wall and adjacent tissue If the egg is very close to the surface epithelium it quickly breaks into the lumen If it is deeper in the tissues it produces a tiny abscess which may rupture into the lumen The egg reaches water in urine or feces and soon hatches, liberating a free swimming embryo

Development in the Snail. The embryo or miracidium is a ciliated actively swimming organism It remains infective without feeding for about six to eight hours after hatching during which time it must reach and penetrate a suitable fresh water snail if further development is to occur (see Table X 1 p 643 for the known snail hosts) In the snail the miracidium becomes transformed into a *mother sporocyst*, which in turn produces many *daughter sporocysts* These migrate to the gonad and

ce hundreds or

ich escape from

to eight weeks

elapse from the penetration of the miracidium to the liberation of cercariae in *S mansoni* under optimum conditions only four weeks are necessary *S japonicum* requires five to seven weeks (Fig VII 61)

Penetration of Cercariae. Upon emerging from the snail the cercariae swim about vigorously tail first and, after reaching the surface

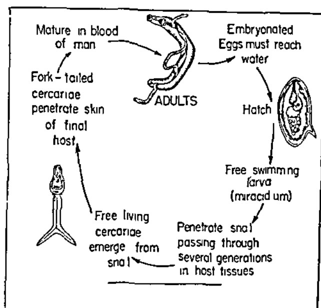


Figure VII 61 Trematode cycle—schistosome type

of the water gradually sink to the bottom This behavior is repeated many times although some cercariae (especially those of *S japonicum*) may remain temporarily attached to the surface film by their suckers

Persons engaged in occupations in endemic areas which necessitate contact with water for example growing rice washing clothes or vehicles may acquire schistosomiasis Drinking infested water or bathing or

ora

of

occur within five minutes It is aided by enzymes from the penetration glands By the end of 24 hours the larvae have worked their way through the epidermis to the peripheral venules they are then carried through the blood stream to the right side of the heart and thence to the pulmonary capillaries where they may be delayed for several days while squeezing through the lumen of the capillaries into the veins The parasites then journey back through the left side of the heart into the systemic circulation It is believed that only those survive which pass through the mesenteric arteries and capillaries and reach the portal circulation Here they develop rapidly feeding on the nutritious portal blood and soon crawl back into the larger portal venules Copulation occurs before the parasites are fully mature Subsequently the females mature and the males carry them into the mesenteric or pelvic venules where they deposit their eggs

Reservoir Hosts In many areas man serves as the principal host for both *S haematobium* and *S mansoni* Monkeys and certain rodents can be infected experimentally with both species The peccary also has been infected in the laboratory with *S mansoni* Baboons and monkeys

have been found naturally infected with *S mansoni* and *S haematobium*, and a rodent infected in nature with *S mansoni* has been found in Africa These animals may prove to be important reservoir hosts in certain areas *Schistosoma japonicum*, in addition to infecting man, parasitizes water buffalo, horses, cattle, pigs, dogs, cats and field rodents, some of which serve as important reservoir hosts

Several other species of schistosomes have been reported infrequently as parasites of man One is *S spindale*, a parasite of cattle sheep, goats, horses and antelopes of India, South Africa and Sumatra Some workers

Host Response

The pathology and clinical manifestations of schistosomiasis are essentially the same for all three species of worm, differing only in the worms location and egg-laying capacity The disease can be divided into three stages (1) invasion and maturation of the worms, (2) egg deposition and excretion, and (3) tissue proliferation and scar formation or repair There is usually overlapping of these stages

In penetrating the skin the cercariae secrete an enzyme from their cephalic glands Itching and urticaria may occur and be followed by a red papular eruption lasting several days Dermatitis is a more prominent feature of the infection and is caused by the cercariae of schistosomes of rodents and birds which cannot develop to maturity in man (see p 513)

In the migration of the young worms through the lungs and mesenteric vessels, some of them undoubtedly rupture capillaries and cause minute hemorrhages This has been demonstrated in experimental animals but has rarely, if ever, produced recognized symptoms in man

As the worms mature in the portal and mesenteric veins they apparently become antigenic as foreign proteins About a week before the first eggs are extruded by the female worms, that is, about three to ten weeks after exposure, the infected person begins to have a daily afternoon rise of temperature falling to normal the next morning, malaise, and sometimes epigastric discomfort and a slight cough There is often extensive urticaria in large patches on various parts of the body Aus-

as Yangtze River fever or urticarial fever before they were recognized as the first stage of schistosomiasis

The second stage begins with the deposition of eggs in the tissues The miracidium within the egg quickly matures and survives for about three weeks During this period it secretes an enzyme which produces a minute abscess containing mainly polymorphonuclear leukocytes, many of which are eosinophils If a mass of eggs is deposited together the abscess may be of considerable size and may have an area of necrosis at the center Abscesses and small ulcers develop in the walls and on the mucosal

surfaces of the intestine or bladder and eggs which are carried by the blood stream as emboli to the liver or lungs produce abscesses where they lodge The liver becomes enlarged and the *resulting portal ob* struction leads to enlargement of the spleen The eggs add to the foreign protein reaction of the host The urticaria and pulmonary signs usually persist for only five to seven days but the fever continues and the eosinophilia increases often reaching 60 to 80 per cent of the total leuko cytes In severe cases there may be a considerable increase in the blood serum globulin This acute reaction lasts for about three to ten weeks the temperature gradually returning to normal There may be exacerba tions however and egg deposition will continue during the life of the female worms which is known to be sometimes as long as 30 years

The third stage that of tissue proliferation and repair begins with the healing of the acute abscess The polymorphonuclear leukocytes are replaced by epithelioid cells forming a pseudotubercle Foreign body giant cells appear and surround and invade the dead egg Ultimately the egg may become calcified or may disappear entirely and normal struc ture returns or a scar *is formed Thickening of the wall of the intestine* or bladder occurs with polyp formation on the mucosal surface and adhesions on the peritoneal surface In the liver obliteration of many portal venules leads to a true portal cirrhosis It is possible that nutri tional deficiency adds to the cirrhosis in the late stages of the disease In the lungs scarring may lead to obstruction of the pulmonary circulation and result in cor pulmonale There is no good evidence that toxic sub stances from the adult worms themselves contribute to the fibrosis which is the end result of the infection

Other anastomoses besides those of the hemorrhoidal plexus which is the normal path of migration of *S haematobium* into the pelvic veins may permit the migration of adult worms and the deposition of eggs in unusual situations Anastomoses between portal and hepatic venules in the liver may be large enough *to permit the direct passage of eggs* to the lungs and anastomoses between the larger mesenteric veins and the vena cava may permit the passage of both eggs and worms into the vena cava *and lungs especially if portal obstruction causes these* anas tomoses to enlarge There are also anastomoses between the lower colonic veins and those of the spinal column through which adult worms can *gain access to the central nervous system* and deposit eggs in the spinal cord or the brain Other ectopic locations where worms have been known to deposit eggs are the conjunctiva and skin

Immunity to superinfection has been demonstrated in experimental animals especially in monkeys It is probable that the same thing hap pens in man and that a light initial infection will prevent later exposures from resulting in an ultimate heavy infection Antibodies to antigens produced from cercariae adult worms and eggs have been demonstrated in serologic and intradermal reactions but the relation of these antibodies to immunity has not been clearly demonstrated

Diagnosis

Specific diagnosis of schistosomiasis depends mainly upon the demon stration of the characteristic *eggs from the feces* or urine (see pages

809–811 for details) In cases of schistosomiasis mansoni or japonica rectal or sigmoidoscopic biopsies are of value if eggs cannot be found in the feces In schistosomiasis haematobia biopsied material may be obtained through the cystoscope The biopsy specimen should first be pressed out between two slides and examined under low magnification If eggs are present they should be observed under high power to determine whether they are alive If alive the miracidium will be seen to move or a flaglike motion of its excretory "flame cells can be observed In treated cases dead eggs persist for a long time and their presence should not be interpreted as an indication that further treatment is necessary The biopsy specimen can finally be fixed in formalin for permanent record or for sectioning Complement fixation and intradermal tests with extracts of cercariae as antigen give reactions specific for the schistosome group but not always for the species They may be used in doubtful cases or to follow the effects of treatment but are not practical for ordinary use The intradermal test gives an immediate type of hypersensitive response It has been used in surveys of prevalence where fecal or urine specimens are difficult to obtain An eosinophilia should lead to a suspicion of schistosomiasis in any person who may have been exposed in an endemic area

Treatment

General Considerations Trivalent compounds of antimony are useful for the treatment of schistosomiasis Pentavalent compounds are not effective

Potassium antimony tartrate (tartar emetic) or the sodium salt are most effective Both must be administered intravenously with great care The needle should be wiped with a sterile sponge and none of the solution should be allowed to escape into the surrounding tissue if a painful necrosis is to be avoided A 0 5 per cent solution in 5 per cent glucose physiologic saline or distilled water should be used It can be sterilized by gentle boiling for five minutes but *must not be autoclaved* Injections should be given very slowly not faster than 3 to 4 ml per minute on alternate days Dosage schedule should be as follows 8 12 16 20 24 28 ml (0 4 to 1 4 grams tartrate) then 28 ml for nine to 12 more injections (total 1 8 to 2 2 grams) depending on the species of worm *S japonicum* is the most resistant to treatment To avoid toxic reactions the best time to give injections is two to three hours after a light meal and the patient should remain recumbent for at least an hour afterward Doses for persons weighing less than 50 kg should be calculated in proportion to weight

Toxic reactions consist of nausea vomiting epigastric distress conjunctivitis peripheral neuritis dizziness faintness precordial constriction and transient electrocardiographic changes in the S T segment Severe toxicity may result in circulatory collapse and sudden death

[illegible] can be minimized by very

slow administration Muscle and joint aching is common but does not usually require interruption of treatment A syringe with epinephrine solution should be at hand in case of severe immediate reaction

Stibophen (Fuadin neoantimosan antimony pyrocatechin disulfonate) can be administered intramuscularly It is supplied in a 6 3 per cent solution Recommended dosage is as follows first day 1 5 ml second day 3 5 ml third day 5 0 ml thereafter 5 0 ml on alternate days for 18 injections—a total of 100 ml This will cure practically all cases of *S haematobium* and *S mansoni* infections but only about 40 per cent of even light *S japonicum* infections There is no coughing associated with these injections but nausea vomiting and muscle and joint aching are frequent If reactions are severe the dose should be reduced

Anthiomaline (lithium antimony thiomalate) and sodium antimony gluconate (Pentostam) have been employed but are less effective and fully as toxic as tartar emetic or stibophen

Contraindications In patients with acute febrile diseases of other origin treatment with antimony compounds should be postponed In the presence of severe liver kidney or cardiac insufficiency these drugs should be given with great caution and the patient's condition should be watched carefully to detect unfavorable reactions

Criteria of Cure Patients should be examined at intervals of one or two months for a year in order to detect relapses The finding of living eggs in the feces or urine is an indication for retreatment with a larger total dose Reinfection must be considered a possibility in endemic areas and treated patients should be educated to avoid reexposure

Prophylaxis

Theoretically the schistosomes are vulnerable to attack in all stages of their life cycles The adults can be attacked by chemotherapy This has been attempted in Egypt and has diminished the severity of the disease in many cases but has not materially reduced the prevalence of infection The miracidia can be prevented from reaching snails by proper storage or disposal of excreta The snails can be attacked by chemical molluscicides Copper sulfate has been used in Egypt for many years with partial success and sodium pentachlorophenate introduced since World War II has proved promising in limited endemic areas in Japan and elsewhere (see page 642) The advantages of the use of such compounds must be weighed against the temporary elimination of fish which are important as a source of protein in the diet The cercariae can be prevented from penetrating man by avoiding entrance into infested water or by storage or chlorination of water A combination of methods will be necessary in most endemic areas and education of the people in changing long established habits and methods of working will also be necessary Where animal reservoir hosts are involved prevention of human infection will be more difficult

Schistosomiasis Haematobia

Synonyms. Urinary bilharziasis, schistosomal hematuria, endemic hematuria, vesical schistosomiasis

Definition. *Schistosomiasis haematobia is due to the presence of the* blood fluke, *Schistosoma haematobium* in the vesical and pelvic venous plexuses of man The disease is frequently accompanied by severe hematuria and cystitis

Distribution. Schistosomiasis haematobia occurs throughout much of Africa and the Middle East and in isolated areas of southern Europe (Portugal and Cyprus) The total number of infections has been estimated at 39 million *The Nile Valley is one of the chief endemic centers* of the disease The infection also occurs across North Africa to Morocco and down the eastern side (Somaliland Uganda, Kenya, Tanganyika, Mozambique, Nyassaland North and South Rhodesia Union of South Africa and the islands of Madagascar, Mauritius and Reunion) It occurs extensively in the Gold Coast and parts of the Belgian Congo In the Middle East it is endemic in parts of Israel, Northern Syria, Arabia, Iran and Iraq (*mostly along the Tigris and Euphrates valleys*) *More* recently the disease was reported from Yemen India (Bombay state) and Liberia (Fig VII 62)

Etiology. *Morphology* *Schistosoma haematobium* (Bilharz 1852) Weinland 1858 inhabits the vesical and pelvic plexuses of the

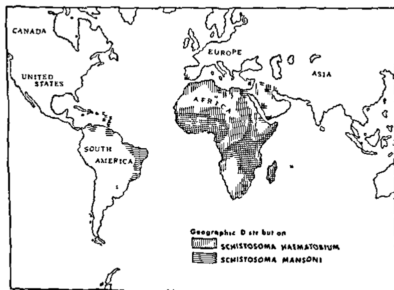


Figure VII 62 Geographic distribution of *Schistosoma haematobium* and *S mansoni* (Courtesy of History of the Medical Department in World War II From Ferguson and Bang s chapter on Schistosomiasis)

venous circulation and the veins of the lower colon and rectum The cuticle of the male is covered with small tubercles that of the female possesses minute papillae which are limited to either extremity of the worm In the male four or five testes are located just posterior to the ace tabulum In the female the ovary is located posterior to the middle of the body There is a correspondingly long uterus which may contain 50 eggs at one time The egg is pointed at one end For other details of schistosomal morphology see page 490

Development The life cycle does not differ markedly from the generalized life history outlined on page 491 except that the worms migrate from the mesenteric to the pelvic veins and the eggs are discharged principally in urine rather than in feces

Epidemiology. Man is the main reservoir for *S haematobium* Baboons and monkeys have been found infected in nature but their importance as a source of infection in various localities is undetermined Embryonated eggs hatch when the urine becomes diluted with fresh water The ciliated miracidia penetrate snails of the genera *Bulinus Physopsis* and *Biomphalaria* in whose tissues mother and daughter sporocysts are formed The latter produce characteristic brevifurcate (short fork tailed) cercariae that penetrate the exposed skin of man

In endemic regions practically the entire population of some communities may be infected Between 11 and 75 per cent of the population of lower Egypt and 33 to 94 per cent of those examined in Tanganyika harbor this fluke The distribution of the disease is increasing owing to the transfer of snails from infected foci to other areas as new irrigation projects are completed The proper snail host when present in non endemic localities may become infected from eggs discharged into canals streams or pools by persons harboring the parasite Transmission in certain Mohammedan countries is facilitated by the religious stipulation that the anal and urethral orifices be washed with water after urination or defecation This custom is usually carried out in a river or canal Another epidemiologic factor is that the species of snails serving as intermediate hosts for the parasite thrive in sewage

The chief intermediate hosts for this parasite in North Africa and the Middle East are fresh water snails of the genus *Bulinus* In Africa south of the Sahara Desert members of the subgenus *Physopsis* serve as hosts and in Portugal the snail host is a member of the genus *Biomphalaria* (Table X 1 p 643)

Pathology The pathologic changes are produced chiefly by the eggs of the worm The urinary bladder is the principal organ involved Eggs are deposited in all layers of the bladder wall and the secretion of the enclosed miracidia produces necrosis and minute abscess formation Eggs in the mucosa can thus easily break through the epithelium into the lumen and with them mucus blood and pus enter the urine leaving minute ulcers in the mucosa Eggs which are deposited deeper in the wall may break through later especially if they are close together and form a larger abscess Others cannot break through and the lesion goes on to pseudotubercle and scar formation Ulceration and irritation of the epithelium lead to polyp formation which may become malignant

Scarring causes thickening of the bladder wall, with loss of elasticity and ultimate contracture Masses of eggs become calcified (Figs VII 63 VII 64), giving the inner surface a sandy appearance, and calculi may form in the lumen Secondary bacterial infection may occur Eggs are often deposited in the ureters, causing obstruction and hydronephrosis or pyonephrosis Eggs may also be deposited in other pelvic organs, such as the seminal vesicles, prostate, urethra, spermatic cord or penis in men and the uterus, vagina and vulva in women Even the cutaneous venules may be invaded, with eggs breaking out through the skin Although some eggs are deposited in the wall of the lower colon and some are carried to the liver, they are rarely numerous enough to produce significant lesions in these locations Lesions resulting from the migration of the worms and deposition of eggs in the brain spinal cord and conjunctiva have also been reported Many eggs are carried by the blood stream to the lungs, with resulting lesions Obstruction to the pulmonic circulation may lead to right sided heart failure The association of bladder carcinoma and S *haematobium* infections is well known In Egypt, cancer of the bladder has been reported to occur more frequently in infected than in uninfected groups

Clinical Characteristics. The incubation period is usually ten to 12 weeks The early symptoms of evening fever followed by sweating



Figure VII 63 Bladder polyp in schistosomiasis haematobia Note shallow ulceration of surface mucosa many eggs and minute abscesses in submucosa cross section of a pair of adult worms in venule of submucosa (Ash and Spitz Atlas of Pathology of Tropical Diseases)

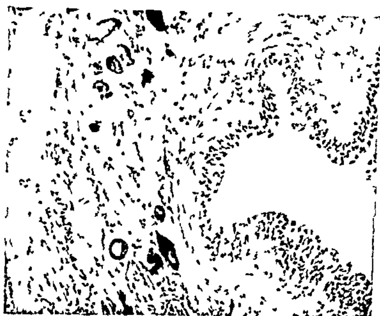


Figure VII 54 Schistosomiasis fibrosis of bladder wall eggs of S haematobium

lassitude abdominal discomfort and urticaria vary greatly in individual cases The fever may last for several weeks and then gradually subside Urinary frequency is a common early symptom and may be accompanied by a scalding sensation along the course of the urethra during and after voiding In natives of endemic areas hematuria may be the first symptom noticed It is frequently gradual in onset at first microscopic later becoming gross as frank ulceration of the bladder mucosa develops At first it is terminal in character With extensive ulceration the whole specimen may be bloody and clots may be present Pain is variable and is usually referred to the suprapubic region or the perineum Often it is aggravated by distention of the bladder and is most intense at the end of micturition

In late cases symptoms of ascending pyogenic renal infection or neoplasia may appear Urinary obstruction due to scarring or prostatic hypertrophy may occur

Diagnosis The finding of terminal spined eggs in the urine is pathognomonic of this disease These are passed with the last few drops of the urine at the end of micturition The eggs are easily seen under low power of the microscope

Cystoscopy will reveal bleeding points minute ulcers and in late cases sandlike excrescences which are usually calcified Biopsy specimens should reveal eggs Eggs may also be found in the feces and seminal fluid Frequently rectal or sigmoid biopsies reveal eggs most of the eggs in the biopsied material are not viable

Treatment Stibophen (Fuadin) is the drug of choice because it can be administered intramuscularly and is curative in adequate dosage A course of treatment for a person weighing 50 to 75 kg should employ

100 ml of the 6 3 per cent solution Others should receive doses in proportion to weight

Potassium or sodium antimony tartrate is more effective than stibophen but less convenient because it must be administered intravenously Total dosage for an adult should be 360 ml of a 0 5 per cent solution (1 8 [illegible]

[illegible]

the prevention of S *haematobium* infection In Moslem countries which comprise most of the endemic regions, the religious requirement of urination defecation and ablution before praying or eating is a great source of infection Water which looks clean may be heavily infested with cercariae In rice growing areas such as Egypt, periodic drainage and drying of the irrigation canals has been used, but the snails can burrow into the soil and survive Clearing vegetation from canals and ponds reduces snail population However, the extension of irrigated areas and the greater mobility of people tend to increase the extent of endemic areas Copper sulfate or copper carbonate (15 to 50 ppm.) has been used in Egypt for many years with only partial success Sodium penta chlorophenate (Santobrite) and related compounds are more effective molluscicides (see p 642)

The improvement of general sanitation, provision of pure water supplies and education of the people can contribute to prevention

Schistosomiasis Mansoni

Synonyms. Manson's intestinal schistosomiasis bilharziasis mansoni intestinal bilharziasis, bilharzial dysentery, schistosomal dysentery

Definition. Schistosomiasis mansoni is an endemic disease with abdominal and dysenteric symptoms and splenomegaly caused by the blood fluke *Schistosoma mansoni*

Distribution. Schistosomiasis mansoni originally was an African disease but subsequently was imported into the West Indies and South America by the slave trade The total number of human infections has been estimated at 29 million It is known to occur commonly in the inhabitants of the Nile Delta, much of the east coast of Africa parts of west Africa the Congo River basin, South Africa and the island of Madagascar It is also present in North Africa (Libya), in Eritrea and in Asia (Arabia [illegible]
Brazil, [illegible]
Caribbe[illegible]
tinique (Fig VII 62, p 497)

Etiology. *Morphology* *Schistosoma mansoni* (Sambon, 1907) superficially resembles S *haematobium*. The tubercles of the cuticle of

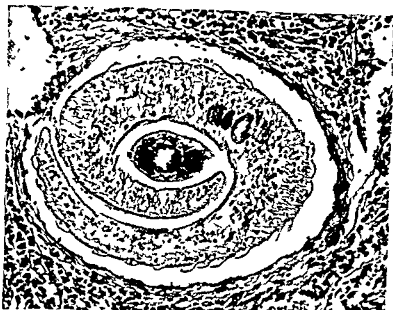


Figure VII 65 Schistosomiasis male and female *S mansoni* in lumen of mesenteric vein showing tuberculate cuticula of male

the male are more prominent than those of *S haematobium* (Fig VII 65) There are six to nine testes In the female the ovary is located anterior to the middle The uterus, which is correspondingly short rarely contains more than one egg The egg is easily identified by its lateral spine

Development The life cycle of *S mansoni* conforms to the gen

[illegible] es

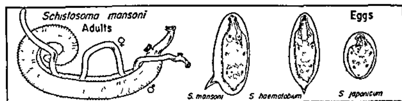
[illegible] (1) different species of snails serve as intermediate host (see Table VI p 643) and (2) defecation rather than urination by infected persons contaminates the water with schistosome eggs Untreated sewage emptying into ditches, streams or lakes constitutes an ever present menace to the populations in endemic regions (Fig VII 66)

The known intermediate hosts of *S mansoni* are all flat fresh water snails of the family PLANORBIDAE In Africa and adjacent countries they belong to the genus *Biomphalaria*, in South America and the West Indies they belong to the genera *Australorbis* and *Tropicorbis* Within a period of about four weeks after penetration by the miracidium cercariae emerge from the snail and are infective for man

Baboons and monkeys have been found to be naturally infected The importance of their role as reservoir hosts in different endemic areas has not been determined It is possible that some rodents may be capable of serving as reservoir hosts, since mice hamsters peccaries and several kinds of wild rodents have been infected experimentally and a wild rodent was found in Egypt infected with sexually immature *S mansoni*

Pathology. The eggs of S. *mansoni* are deposited almost entirely in the capillaries and venules of the large intestine or the lower portion of the small intestine, they may also be carried by the blood stream to

severe disease. The wall of the intestine becomes thickened (Fig VII 67),





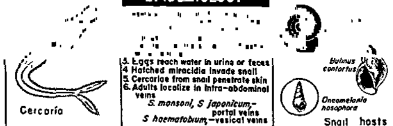


Figure VII 68 Epidemiology of the schistosomiases



Figure VII 67 Schistosomiasis ulceration and fibrosis of colon, eggs of *S mansoni* in submucosa.

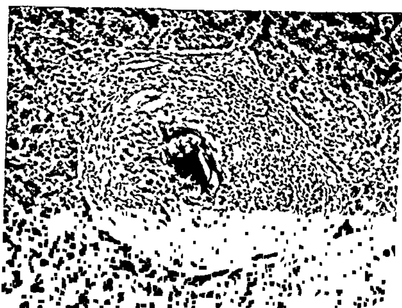


Figure VII 68 Schistosomiasis pseudotubercle in liver foreign body reaction cellular infiltration and early connective tissue proliferation about egg of *S mansoni*

polyps protrude into the lumen and in heavy infections there may be prolapse of the rectum or perianal masses In the liver, scarring leads to *cirrhosis* (Fig VII 68), and portal obstruction causes *splenomegaly* and ascites Anastomoses between the mesenteric-portal veins and the vena cava become enlarged and permit eggs, and even worms, to be carried to the lungs, where fibrosis may cause obstruction to the pulmonary cir-

culation and lead to right ventricular failure Worms may also migrate to the spinal cord and deposit eggs which produce lesions resulting in paralysis

Clinical Characteristics The penetration of the cercariae may cause itching followed by a papular rash in sensitized individuals The worms mature in about five weeks Toward the end of this time there is a gradual onset of fever and malaise often with upper abdominal discomfort and nausea Urticaria may occur Egg deposition and excretion begin a week later In Puerto Rico where the early phase of the disease has been studied thoroughly Pons has described two clinical types the dysenteric and the hepatosplenic In the dysenteric type deposition of eggs in the wall of the intestine is accompanied by bloody diarrhea loss of weight abdominal pain and moderate anemia Eggs are abundant in the mixture of blood pus and mucus discharged from the intestine In the hepatosplenic type there is much less diarrhea symptoms of upper abdominal discomfort predominate and there is progressive enlargement of

With the development of fibrosis of the lesions adhesions and polyp formation may give rise to intestinal obstruction or episodes of abdominal pain The progressive cirrhosis of the liver may cause esophageal varices with hematemesis The spleen may become very large Ascites may require paracentesis leukopenia may develop The clinical picture of Banti s disease frequently occurs Hepatic insufficiency may characterize the terminal period Dietary deficiency may also contribute to the liver disease

Eggs carried to the lungs as emboli gradually produce a fibrosis Numerous cases of resulting right ventricular failure have been reported Eggs deposited in the spinal cord produce symptoms suggestive of abscess or tumor

It is believed that numerous exposures to small numbers of cercariae cause much milder manifestations and less ultimate damage than a single exposure to many cercariae because immunity prevents later invading worms from developing into adults

Diagnosis Demonstration of the characteristic lateral spined egg is necess[illegible]
the feces
first more
or blood
cases concentration techniques may be needed to locate the eggs Sedimentation or centrifugation and washing in normal saline will keep the eggs alive and prevent hatching The formalin ether concentration method is convenient but usually kills the miracidium within the egg (p 809)

Proctoscopy may reveal small nodules bleeding points or ulcers from which a biopsy specimen can be obtained It should be pressed out between two slides for observation in order to demonstrate the viability of the eggs In late cases this is especially valuable If eggs cannot be found in clinically suspected cases the complement fixation intradermal or the circumoval test may help to confirm the diagnosis

Treatment Specific treatment with antimony compounds is the same as for schistosomiasis haematobia (see p 495) In late cases with severe liver damage these compounds should be administered with great care because of the danger of hepatic failure In cases resembling Banti s disease or showing evidence of esophageal varices splenectomy may re lieve symptoms by reducing the flow of blood to the liver The operation of portacaval shunt has also been employed with good effect

Prophylaxis *Marisa cornuarietis* a large ampullarid snail com petes in some areas with *Australorbis glabratus* and offers some hope of being useful in biologic control Otherwise the prophylaxis of infection by *S mansoni* does not differ from that for schistosomiasis haematobia (cf p 501)

Schistosomiasis Japonica

Synonyms Oriental schistosomiasis Katayama disease Yangtze River fever

Definition Schistosomiasis japonica is a grave chronic disease en demic in the Far East with abdominal and dysenteric symptoms caused by *Schistosoma japonicum* Man and domestic animals are affected

Distribution Schistosomiasis japonica is found only in the Far East in parts of China Japan Formosa the Philippines and Celebes The total number of human infections has been estimated at 46 million In China large portions of the Yangtze Valley coastal areas from the Yangtze delta to Canton river valleys inland from Canton the Mekong Valley in Yunnan Province and the island of Hainan comprise the endemic areas (Fig VII 69)

In Japan the disease is limited to five small areas These regions and the peak prevalence in the several communities follow the Tone River Valley northeast of Tokyo (10 to 14 per cent) the Numazu coastal area southwest of Tokyo (less than 4 per cent in a single village) the Kofu valley west of Tokyo (0 2 to 66 per cent of 3035 persons and over 90 per cent when multiple stools were examined) the Katayama area of Hiroshima Prefecture (20 to 33 per cent) and the Kurume Tosu area on Kyushu Island (29 to 73 per cent for single stool examinations)

In Formosa the endemic area is limited to the Changhua district on the west coast The infection is caused by a different strain which seems to be limited to domestic and wild animals man being an unsuitable host

Schistosomiasis japonica occurs in the Philippines on the southern tip of Luzon on the northeast side of Mindoro (40 per cent infected) in coastal and inland foci on Sam in the eastern coastal area of Leyte (up to 90 per cent in childre every province on Mindanao ex cept Misamis l (Fig

The Lake Lindoe region of the Celebes is an isolated endemic area of human infection

Etiology *Morphology* Adult *S japonicum* (Katsurada 1904) can be distinguished from the other two human species by the absence of the tuberculated integument Instead the cuticula of both sexes is covered with minute spines The male possesses seven testes the female is characterized by a long uterus which may contain as many as 300 eggs The eggs are broad oval measure 70 to 90 by 50 to 70 μ and may be distinguished by the enclosed miracidium and the rarely detectable small knob on the lateral aspect of the shell (Fig VII 78 p 518)

Development *Schistosoma japonicum* follows the pattern of development described for *S haematobium* and *S mansoni*

Epidemiology Amphibious snails of the genus *Oncomelania* that normally inhabit the banks of irrigation ditches and canals or marshes

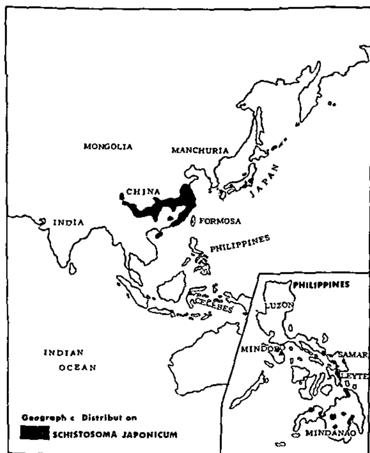


Figure VII 69 Geographic distribution of *Schistosoma japonicum* (Courtesy of History of the Medical Department in World War II From Ferguson and Bang's chapter on Schistosomiasis)

Treatment. Specific treatment with antimony compounds is the same as for schistosomiasis haematobia (see p 495) In late cases with severe liver damage these compounds should be administered with great care because of the danger of hepatic failure In cases resembling Banti's disease or showing evidence of esophageal varices, splenectomy may relieve symptoms by reducing the flow of blood to the liver The operation of portacaval shunt has also been employed with good effect

Prophylaxis. *Marisa cornuarietis*, a large ampullarid snail competes in some areas with *Australorbis glabratus* and offers some hope of being useful in biologic control Otherwise, the prophylaxis of infection by *S mansoni* does not differ from that for schistosomiasis haematobia (cf p 501)

Schistosomiasis Japonica

Synonyms. Oriental schistosomiasis, Katayama disease, Yangtze River fever

Definition. Schistosomiasis japonica is a grave, chronic disease endemic in the Far East, with abdominal and dysenteric symptoms caused by *Schistosoma japonicum* Man and domestic animals are affected

Distribution. Schistosomiasis japonica is found only in the Far East in parts of China, Japan, Formosa, the Philippines and Celebes The total number of human infections has been estimated at 46 million In China large portions of the Yangtze Valley, coastal areas from the Yangtze delta to Canton, river valleys inland from Canton, the Mekong Valley in Yunnan Province and the island of Hainan comprise the endemic areas (Fig VII 69)

In Japan the disease is limited to five small areas These regions and the peak prevalence in the several communities follow the Tone River Valley northeast of Tokyo (10 to 14 per cent), the Numazu coastal area southwest of Tokyo (less than 4 per cent in a single village), the Kofu valley west of Tokyo (0 2 to 66 per cent of 3055 persons and over 90 per cent when multiple stools were examined), the Katayama area of Hiroshima Prefecture (20 to 33 per cent), and the Kurume-Tosu area on Kyushu Island (29 to 73 per cent for single stool examinations)

In Formosa the endemic area is limited to the Changhua district on the west coast The infection is caused by a different strain which seems to be limited to domestic and wild animals man being an unsuitable host

Schistosomiasis japonica occurs in the Philippines on the southern tip of Luzon on the northeast side of Mindoro (40 per cent infected), in coastal and inland foci on Samar, in the eastern coastal area of Leyte (up to 90 per cent in children), and in every province on Mindanao except Misamis Oriental (Fig VII 69)

The Lake Lindoe region of the Celebes is an isolated endemic area of human infection

Etiology. *Morphology* Adult *S japonicum* (Katsurada, 1904) can be distinguished from the other two human species by the absence of the tuberculated integument Instead the cuticula of both sexes is covered with minute spines The male possesses seven testes the female is characterized by a long uterus which may contain as many as 300 eggs The eggs are broad oval measure 70 to 90 by 50 to 70 μ and may be distinguished by the enclosed miracidium and the rarely detectable small knob on the lateral aspect of the shell (Fig VII 78 p 518)

Development *Schistosoma japonicum* follows the pattern of development described for *S haematobium* and *S mansoni*

Epidemiology. Amphibious snails of the genus *Oncomelania* that normally inhabit the banks of irrigation ditches and canals or marshes

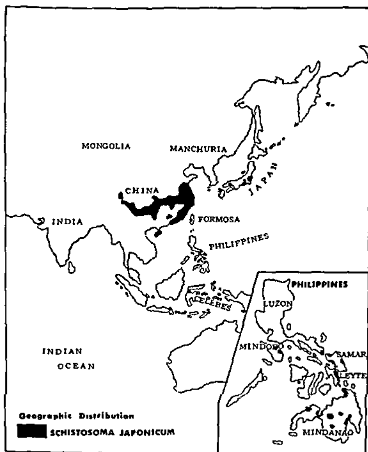


Figure VII 69 Geographic distribution of *Schistosoma japonicum* (Courtesy of History of the Medical Department in World War II From Ferguson and Bang's chapter on Schistosomiasis)



Figure VII 70 Known intermediate hosts of *S japonicum* Reading left to right they are (Top row) *Oncomelania hupensis*–China *O nosophora*–Japan (Bottom row) *O formosana*–Formosa *O quadrasi*–Phillippines (Courtesy University of Florida College of Medicine)

and quiet fresh water serve as the intermediate hosts of *S japonicum* (see Table X I, p 643) These small, slender snails, measuring not over a half inch in length, are usually not known by the local inhabitants Canals, irrigation ditches, marshes, overflow areas, slow-flowing streams and shallow ponds or pools where the snails live are often seeded with eggs in human feces from defecation sites, nightsoil boats or buckets (Fig VII 70)

Human infection results from wading in the shallow water along irrigation ditches, canals, rice fields or rice seedling beds containing cercariae which have emerged from infected snails The infection may also be acquired by bathing, washing clothes or vehicles, or, less frequently, drinking the contaminated water In many cases it is primarily a rice farmer's disease

During the campaign to recapture the Philippine Island of Leyte from the Japanese during World War II over 1500 American troops became infected with *S japonicum* Infantrymen wading through swamps and rice fields, engineers building bridges, and men bathing in fresh water ponds and streams were the chief victims Accurate location of infested areas, posting of danger signs and education of troops were necessary to stop the epidemic

Schistosoma japonicum has a wide variety of reservoir hosts in addition to man Dogs, cats, horses, pigs, cattle, water buffalo, deer, field and other mice and rats may become infected in endemic areas and serve as an additional source of contamination of the water

Pathology. *Schistosoma japonicum* causes a more severe infection than the other two species The female worm extrudes about ten times

as many eggs a day as *S mansoni* The eggs are often extruded in masses and produce abscesses in which there is a large area of necrosis surrounded by polymorphonuclear leukocytes including many eosinophils [illegible]

accompany them into the fecal discharge Proliferation of epithelium between and into abscess cavities leads to polyp formation, and in patients with advanced disease there may be hundreds of these polyps protruding into the lumen Deeper abscesses (Fig VII 71) ultimately heal, producing thickening of the wall, and lesions on the serosal surface (Fig VII 72) produce fibrinous adhesions which become fibrous, causing permanent matting together of loops of intestine Eggs carried by the portal blood stream to the liver likewise cause abscesses and scars (Fig VII 73) which may lead to large areas of fibrosis and obstruction to the portal circulation (Fig VII 74) The liver at first becomes enlarged, but ultimately may shrink with scarring until it is no longer palpable The spleen becomes progressively enlarged from the portal obstruction until it may occupy the entire left half of the abdomen Ascites develops and may become massive Varicose veins may develop in the abdominal wall or in the lower esophagus where fatal hemorrhage may occur

In some heavy infections eggs may be carried through anastomoses in the liver or portacaval vessels to the lungs and produce minute abscesses or pneumonic areas In a small proportion of cases worms may migrate through anastomoses from the mesenteric to the spinal veins and ultimately reach the brain, where their eggs produce abscesses Others have been known to migrate to the cutaneous veins of the trunk where their eggs were discovered in pustular lesions

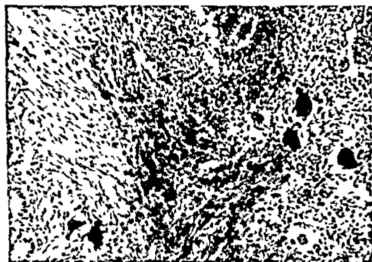


Figure VII 71 Schistosomiasis eggs of *S japonicum* and inflammatory reaction in wall of intestine

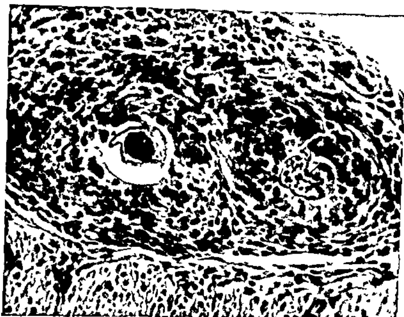


Figure VII 72 Schistosomiasis eggs of *S japonicum* in subserosal fibrous nodule of intestine



Figure VII 73 Schistosomiasis small abscess in liver containing calcified eggs of *S japonicum*

Carcinoma of the colon or liver may occur on rare occasion and has been thought to be initiated by the irritation produced by the eggs

Clinical Characteristics. The worms mature and begin to deposit eggs about four weeks after infection During the week prior to this a



Figure VII 74 Cut su face of the l ver in the case of a heavy infection by *Schistosoma japon cum* (Cour esy of E. C Faust and H. E Meleney in the American Journal of Hygiene Monograph Series No 3 1924)

foreign protein reaction to the worms produces the clinical syndrome originally called Yangtze River fever It consists of afternoon fever malaise dry cough and giant urticaria The lungs show evanescent moist rales Among infected American troops in the Philippines several showed early neurologic symptoms—lethargy or coma mental confusion spastic paralysis involving one or more extremities and abnormal superficial and deep reflexes Only upper neurons appeared to be involved and the spinal fluid was normal Improvement rapidly followed the initiation of treatment but in some cases residual signs lasted for several months Because of the early occurrence widespread involvement of the brain and rapid improvement with treatment it seems probable that these early cerebral manifestations were due to toxic edema of the brain comparable to urticaria rather than to the deposition of eggs in the brain as described below

The deposition of eggs in the walls of the intestine and liver causes continued fever abdominal discomfort right upper quadrant tenderness and severe malaise Eggs appear first in the formed feces but soon there may be diarrhea with blood pus and mucus Increasing leukocytosis occurs with eosinophils sometimes rising to 90 per cent This acute stage may last for eight to ten weeks the fever falling gradually The liver and spleen become palpable early and the former is tender Heavy infections may progress to fatal hepatic failure in less than a year Exacerbations of

mination

In a few cases sometimes previously unrecognized migration of worms to the brain and the deposition of eggs usually in cortical venules produce physical signs of lesions often epileptiform in nature Exploration reveals an abscess containing eggs of *S japonicum* If the disease is suspected from a history of possible exposure or if it is diagnosed either by finding eggs in the feces or by rectal biopsy specific treatment usually eliminates any necessity for surgical intervention and produces rapid improvement and often complete recovery

Diagnosis Definitive diagnosis requires the identification of eggs in the feces or in a rectal biopsy specimen The egg (Fig VII 78 p 518) is about the size and shape of an *Ascaris* egg but differs from it in having a thin wall and usually a fully developed miracidium The rudimentary spine is usually hidden by fecal debris sticking to the egg shell The technique of examination of feces and rectal biopsy is the same as for the eggs of *S mansoni* (see p 505) In the follow up of treated cases numerous dead or calcified eggs may be found in rectal biopsy specimens these are not an indication for further treatment. The complement fixation and intracutaneous tests are of practical value when eggs cannot be found if antigen is available The intracutaneous test has been used to estimate prevalence in an endemic community where it is impractical to obtain fecal specimens Spleen surveys have been used under similar conditions provided malaria is absent

Treatment *Schistosoma japonicum* is more resistant than the other two species to antimony therapy The intravenous administration of so

dium or potassium antimony tartrate is the only effective treatment A total dose of 444 ml of a 0 5 per cent solution (2 2 grams of the salt) is necessary to assure a cure in an adult Fuadin even when given to the limit of tolerance and in repeated courses frequently fails

The serious and not infrequently fatal cerebral complications constitute an imperative indication for the use of tartar emetic intravenously unless the administration of antimony is absolutely contraindicated This will usually alleviate the central nervous system disease and should always be used in preference to surgical intervention Permanent sequelae are twice as common in operated cases as in those receiving one or more courses of tartar emetic (For details of treatment see p 495)

Prophylaxis Prophylaxis does not differ materially from that described for other schistosomiases but the existence of several important animal reservoir hosts makes the problem of prevention more difficult The vast extent of the endemic foci and of the distribution of the snail hosts makes the use of molluscicides difficult except in small areas such as those in Japan A combination of molluscuciding composting of human excreta and other control measures and the cooperation of the people is essential to any progress in prevention (cf p 642)

Schistosome Cercarial Dermatitis

Etiology and Epidemiology The cercariae of approximately 20 species of nonhuman schistosomes mostly adult in birds or small mam

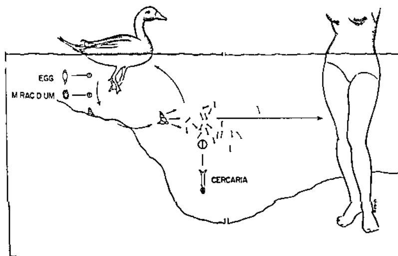


Figure VII.75. Life cycle of a bird schistosome showing how man may acquire swimmer's itch. (Partly after Miller courtesy of The University of Florida College of Medicine)

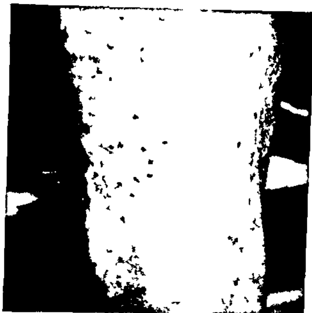


Figure VII 76 Schistosome dermatitis—papular eruption on leg (Courtesy of Dr D B McMullen Walter Reed Army Institute of Research)

mals are known to penetrate the skin of man and produce a dermatitis Depending upon the circumstances under which the disease is acquired it has been variously designated as swimmers itch schistosome dermatitis "clam diggers itch sawah itch or "koganbyo In all cases it involves the association of man and potential intermediate snail hosts infected from the droppings of bird or mammal hosts harboring the parasites (Fig VII 75)

Schistosome dermatitis is widely distributed throughout the fresh water areas of the Americas and has been reported from Alaska Canada many parts of the United States Mexico El Salvador Colombia and Argentina It is highly endemic in Canada Michigan Wisconsin and Minnesota and occurs from sea level to over 9000 feet elevation (Colorado) Elsewhere outbreaks have occurred in Wales Germany France The Netherlands Switzerland Malaya New Zealand Africa and Japan

Until recently it was known only in fresh water but now it has been reported in the brackish and coastal waters along the Atlantic seaboard the Gulf Coast southern and lower California and Hawaii

The fresh water mollusks that serve as intermediate hosts include species of *Lymnaea Helisoma (Planorbis) Physa Polypylis Gyraulus*

Clinical Characteristics

sponses of unsensitized and sensitized individuals to the penetration of the skin by the cercariae of nonhuman schistosomes Initial exposures to these cercariae produce only mild transient reactions that often pass unnoticed Even so many persons experience a prickling sensation as the

water evaporates and the parasites penetrate the skin Macules usually

erythema vesicle formation edema and pruritus which may persist for a week or ten days (Fig VII 76) Reactions vary markedly not only because of differences in susceptibility of the host but also because the nonhuman schistosome cercariae differ markedly in their ability to produce a response in the human host

Treatment consists of palliative topical applications accompanied in severe cases by injections of an antihistamine

Control Control of the fresh water snail host is possible in some areas by treating infested bathing areas with 1 lb of 10 per cent fresh lime and 2 lb of copper sulfate snow per 1000 square feet of bottom Sodium pentachlorophenate should also prove effective

51

Trematodes Exclusive of Schistosomes

Morphology

Introduction The similarity in pattern structure and physiology of most trematodes exclusive of the schistosomes warrants their consideration as a group Despite individual differences in their life cycles these trematodes all gain entrance to man through the digestive tract Each first parasitizes a snail then encysts on vegetation or in some aquatic animal which is subsequently ingested by man

Morphology of Adults All trematodes of man are nonsegmented bilaterally symmetrical and with the exception of the schistosomes hermaphroditic As a rule these parasites are leaflike flattened dorsoventrally range in length from a few millimeters to several centimeters and possess two suckers with which they attach themselves to the mucosa or other tissues of their host The anterior or *oral sucker* surrounds the mouth the ventral one or *acetabulum* is merely a holdfast device The body surface is covered by a thin noncellular cuticle secreted by the underlying cells In some species this cuticula may be spined

The digestive tract opens through the oral sucker into a muscular pharynx followed by an esophagus which bifurcates to form the two lateral intestinal ceca or crura (Fig VII 77) In some species such as *Fasciola hepatica* the crura may be highly branched. The excretory system has two main lateral ducts which empty into a posterior terminal

excretory bladder this in turn opens externally through an excretory pore The nervous system is also bilaterally symmetrical

The reproductive systems are extremely complex The male system usually consists of two testes drained by *vasa efferentia* into a single *vas deferens* This empties through a ventrally situated genital pore near and usually anterior to the acetabulum The terminal portion of the male system is modified to form a muscular copulatory device or *cirrus*

The female reproductive system includes a single *ovary* which gives rise to the *oviduct* The oviduct complex includes a blind seminal receptacle which sometimes drains to the exterior through a dorsal *Laurer's canal* ducts from the laterally situated yolk glands or *vitellaria* and a *shell gland* which empties into the coiled *uterus* This latter structure stores the eggs until they are discharged through a genital pore beside that of the male system into the common genital sinus The lower portion of the uterus serves as a *vagina* Fertilization takes place in the oviduct In rare instances (as in the HETEROPHYIDAE) the genital pore is surrounded by a muscular genital sucker (*gonocotyl*)

Trematode Eggs Eggs of all the trematodes except those of the schistosomes which are spined or knobbed possess a lid or *operculum* which opens to allow the ciliated free swimming *miracidium* to emerge As a rule the eggs are undeveloped when passed in a stool containing only the fertilized zygote and a yolk mass However in some species such as *Clonorchis* and *Heterophyes* each egg contains a fully developed miracidium when evacuated by the host (Fig VII 78)

Group Characteristics Because of the morphologic similarity displayed by the various trematodes a brief summary of their group characteristics may prove more useful than a key

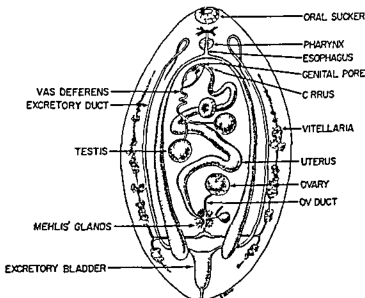


Figure VII 77 Morphology of a typ cal digenetic trematode (Modified from various authors courtesy of University of Florida College of Medicine)

Members of the FASCIOLIDAE infecting man are large trematodes averaging more than 25 mm in length and producing eggs 150 by 90 μ their cercariae encyst on vegetation In members of the genus *Fasciola* (*F hepatica* and *F gigantica*) the dendritic testes are arranged in tandem these together with the intestinal ceca and vitellaria are profusely branched almost entirely filling the posterior two thirds of the worm with their ramifications

Fasciolopsis buski which bears a superficial resemblance to *F hepatica* belongs in a different taxonomic subdivision of the FASCIOLIDAE *Fasciolopsis buski* possesses dendritic testes but has straight unbranched intestinal crura The eggs of the FASCIOLIDAE are undeveloped when laid and are approximately the same size However the operculum on the ovum of *Fasciolopsis buski* is smaller than that on the egg of *F hepatica*

The HETEROPHYIDAE infecting man are all small ovoidal pyriform or elongate trematodes (1 to 3 mm long) which produce minute embryonated eggs that average nearly 30 μ in length The chief human representatives of this family are *Heterophyes heterophyes* and *Metagonimus yokogawai* They are intestinal parasites

Clonorchis sinensis the Oriental liver fluke is classified in the OPISTHORCHIDAE which also includes other liver flukes of man and carnivores (*Opisthorchis viverrini* and *O felineus*) This slender trematode of man ranges between 18 and 40 mm in length It is further characterized by dendritic testes arranged posteriorly in tandem and by the unbranched intestinal crura which extend to the posterior tip of the worm

The Oriental lung fluke *Paragonimus westermani* of the family TROGLOTREMATIDAE is thicker than the others broader and more generally ovoid Although the intestinal crura are straight the lobate testes are roughly opposite one another in the posterior third of the body The ovary is in the midregion and to one side of the acetabulum The American species *P kellicotti* is believed by some workers to be identical with *westermani* which if true would indicate that this fluke is well established in the mammals of North America

Other parasites of man which might be encountered in some areas include the spiny collared or echinostome group and *Gastrodiscoides* ...minis

Generalized Cycle

Oviposition The trematodes mentioned above have similar life cycles The eggs are discharged in the feces except those of *Paragonimus westermani* many of which are eliminated in the sputum the remainder being passed in the stool All the eggs are undeveloped when laid except those of *Clonorchis sinensis* *Heterophyes* spp *Metagonimus yokogawai* and *Opisthorchis* spp which contain ciliated embryos All must reach water and in the case of undeveloped eggs must undergo a period of incubation before hatching the miracidium

Snail Host. Eggs or hatched miracidia must reach a specific snail host within a few hours if the parasites are to survive In the tissues of this host the miracidium becomes transformed into a *mother sporocyst* which then produces a generation of *rediae* and in some cases

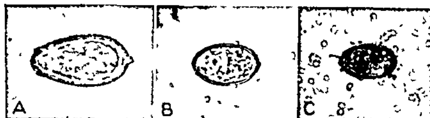


Figure VII 78

daughter rediae Finally, free-living *cercariae* develop and emerge, these in turn, must reach a suitable plant or animal host if they are to survive

The Resting or Metacercarial Stage. Encystment occurs if the liberated cercariae are successful in reaching a suitable resting place In cases where cercariae penetrate tissues of such hosts as fish or crustacea there is a marked host reaction Typically, all encysting cercariae produce an inner cyst wall from secretions of their own cystogenous glands which is soon surrounded by an outer cyst wall of host tissue After varying intervals a reorganization or growth of these larvae leads to the formation of resting stages, or *metacercariae*, which soon are ready to infect man (Fig VII 79)

The cercariae of *Fasciola hepatica* seek various grasses, while those of *Fasciolopsis buski* encyst on water chestnuts, caltrops, hyacinths and the like In the case of the liver flukes *Clonorchis* and *Opisthorchis* spp, and the intestinal flukes *Heterophyes heterophyes* and *Metagonimus yokogawai*, the cercariae seek certain species of fish, and most of them penetrate beneath their scales and reach the musculature before encyst

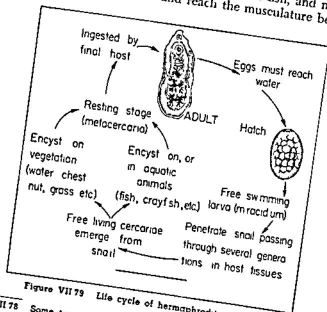


Figure VII 79 Life cycle of hermaphroditic trematodes

gure VII 78 Some trematode eggs A Chinese liver fluke *Clonorchis sinensis* B rophyes heterophyes C *Metagonimus yokogawai* D Lung fluke *Paragonimus wester* E Vesical blood fluke *Schistosoma haematobium* F Oriental blood fluke *Schisto- japonicum* G Manson s blood fluke *Schistosoma mansoni* H Large intestinal fluke *olopsis buski*. All figures 500× except A, which is 830× (Fig A courtesy of Dr E. C in Brenemann Practice of Pediatrics W F Prior Co Figs B and C courtesy of W Shatterly MSC School of Aviation Medicine Gunter AFB Alabama All others y of Dr R L. Roudabush, Ward s Natural Science Establishment Rochester New photos by T Romaniak)

Table VII.10. Reservoirs of the Intestinal, Liver and Lung Trematodes

SPECIES OF TREMATODE	HOSTS	TYPICAL LOCATION IN HOST
Intestinal Flukes		
Fasciolopsis buski	Pig and man	Duodenum, jejunum
Echinostoma ilocanum	Dogs, cats, rats, monkeys and man	Small intestine
Echinochasmus perfoliatus	Dogs, cats, pigs, fox and man	Small intestine
Heterophyes heterophyes	Cat, dog, fox and man	Small intestine
H katsuradai	Man	Small intestine
H brevicaeca	Man	Small intestine
Metagonimus yokogawai	Cats, dogs, pigs, mice (experimental infection), pelicans and man	Small intestine
Gastrodiscoides hominis	Pigs, "mouse deer" (*Tragulus napu*), man	Cecum and colon
Liver Flukes		
Clonorchis sinensis	Dogs, cats and man	Biliary passages
Opisthorchis felineus	Dogs, cats and man	Biliary and pancreatic passages
O viverrini	Dogs, cats and man	Biliary passages
Fasciola hepatica	Sheep, cattle, wild rabbits, hares other herbivores, and man	Liver and biliary passages
F gigantica	Cattle, water buffalo, other herbivores, man	Biliary passages
Dicrocoelium dendriticum	Cattle, goats, horses, donkeys, deer, hares, rabbits, pigs, dogs, covpu, camels and man	Biliary passages
Lung Flukes		
Paragonimus westermani	Tigers, cats, wild cats, panthers, foxes, wolves, dogs, rats, pigs, weasel (*Mustela melampus*), *Lutreola itatsi itatsi*, pencilled cat (*Nyctereutes procyonides*) and man	Lungs
P kellicotti	Mink, pigs, dogs, muskrats, opossum, cats, wild cats goats and man	Lungs

ing The cercariae of the lung fluke, *Paragonimus westermani,* enter fresh water crabs and crayfishes and encyst throughout their bodies

The Final Host. In all cases, infection of man results from the ingestion of raw or inadequately cooked vegetation, fish or crustaceans which serve as the "transfer agents" or intermediate hosts for these parasites

Location in Man *Fasciolopsis buski, Heterophyes heterophyes, Metagonimus yokogawai* and *Echinostoma ilocanum* are intestinal parasites of man *Clonorchis sinensis, F. hepatica, Opisthorchis* spp and *Dicrocoelium dendriticum* localize in the bile ducts, *P westermani,* after migrating through the body, usually reaches the lungs where it becomes encapsulated

Many mammals other than man serve as reservoir hosts for the intestinal, lung and liver flukes The more important of these are summarized in Table VII 10

Diseases Caused by Intestinal Trematodes

Fasciolopsiasis

Synonym *Fasciolopsis buski* infection

Definition Fasciolopsiasis is due to the presence of the giant intestinal fluke *F buski* in the duodenum or jejunum and more rarely in the pylorus or the colon of man The parasites may produce local areas of inflammation and sometimes ulceration and hemorrhage

Distribution *Fasciolopsis buski* occurs commonly in pigs and man in certain areas of eastern Asia particularly in central and south China extending as far north as the Yangtze Valley It is highly endemic in the Chinese provinces of Kwangtung and Chekiang The disease has also been reported in Formosa Annam Tonkin Pakistan Thailand Assam the Malay archipelago Sumatra and Borneo

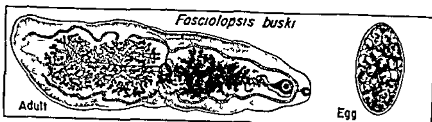
Etiology *Morphology* *Fasciolopsis buski* (Lankester 1857) Odhner 1902 the large intestinal fluke is 50 to 75 mm long when extended It is fleshy often broadly ovate and possesses a spined integument A cephalic cone such as occurs in the genus *Fasciola* is lacking although the oral sucker and ventral sucker (acetabulum) are close together (Fig VII 80) The latter is about four times as large as the oral sucker and measures 2 to 3 mm in diameter The intestinal ceca are unbranched the dendritic testes lie in the posterior half of the body and are arranged in tandem The small vitelline follicles extend from the acetabular region to the posterior tip

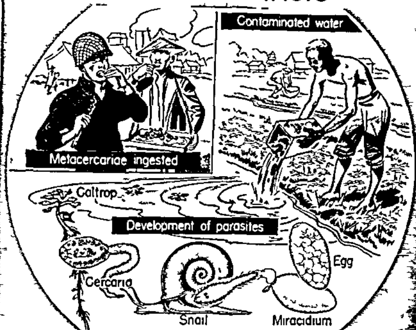
Development Although the adult parasite produces eggs ranging from 67 by 43 to 181 by 95 μ the majority are large eggs between 130 and 140 μ in length and 80 and 85 μ in breadth These are undeveloped

Segmentina or possibly *Gyraulus* which it penetrates It then transforms into a mother sporocyst this in turn produces two generations of rediae The daughter rediae produce free living cercariae 30 to 50 days after the miracidium has penetrated the snail

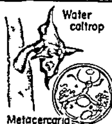
The cercariae encyst on almost any aquatic plant although water caltrops hyacinths chestnuts and bamboos usually serve as "transfer hosts As many as 1000 metacercariae have been found on a single nut or root The metacercariae are very resistant and will survive for a year or more if kept moist desiccation however soon destroys them When an infected root or bulb is eaten and the metacercariae are ingested by the definitive hosts the parasites excyst in the intestine and develop into mature flukes within a month

Epidemiology Infection by *F buski* results from the ingestion of viable metacercariae on the uncooked stems bulbs or fruits of edible water plants The more important plants and the areas where they are particularly prevalent appear in Table VII 11





EPIDEMIOLOGY



1 Reservoir man, pig, rarely dog
2 Undeveloped eggs in stools
3 Fecal contamination of ponds
4 Intermediate hosts
Certain fresh-water snails
5 Cercariae encyst on aquatic plants
6 Ingestion of metacercariae on caltrop, "water-chestnut"
7 Adults in intestine



Figure VII.80 Epidemiology of fasciolopsiasis

The red water caltrop, *T natans* is probably the most heavily infested since it is cultivated for market in artificial ponds fertilized by nightsoil or by defecation directly into the water The plants growing wild in the canals and rivers are less heavily infested *Both the water caltrops and* so called water chestnuts are sold fresh in the Chinese markets during the summer months, and it is then that man becomes infected It is a

Table VII 11. Species of Plants Carrying *Fasciolopsis buski* Listed by Countries

COUNTRY	SPECIES OF PLANT
China Chek ang Prov	Red water caltrop *Trapa natans*
Kwangtung Prov to Yangtze R South China	Water chestnut *Eliocharis tuberosa*
Pakistan Thailand	Water caltrop *Trapa bicornis*
Formosa	Water caltrop *Trapa bispinosa* Water chestnut *Eliocharis tuberosa* Water hyacinth *Eichhornia crassipes*

common practice to peel off the external covering with the teeth and eat the succulent inner parts raw Many metacercarial cysts may be ingested in this way Since desiccation destroys the parasites only fresh plants are dangerous and infection is less frequent when these have been allowed to dry However in the markets vendors of caltrops and nuts often maintain the freshness of their wares by sprinkling them with water a custom which prevents the drying of the cysts (Fig VII 80)

Many different species of snails serve as first intermediate hosts for *F buski*, the principal ones being *Segmentina hemisphaerula* and *Hippeutis cantori*, although developmental stages have been found in *Gyraulus saigunensis*

Pathology. The parasites are usually attached to the mucosa of the duodenum or jejunum less often they are found in the region of the pylorus or in the colon Localized inflammation followed frequently by ulceration occurs at the site of attachment and when deep erosions are produced hemorrhage may occur As many as 3721 adult specimens have been recovered from one patient at autopsy and more than 10 000 by anthelmintic medication The metabolic products of the worm are probably toxic and capable of being absorbed by the host Many patients show a leukocytosis with an eosinophilia up to 34 per cent, in others there may be a lymphocytosis

Clinical Characteristics. The incubation period of fasciolopsiasis lasts 30 to 40 days In cases of light infection it may be asymptomatic, or there may be diarrhea and abdominal pain which may simulate duodenal ulcer The diarrhea often alternates with periods of constipation Later the stools become greenish yellow and contain much undigested food Ascites anorexia nausea and vomiting may occur in severe infections In the final stage of the disease edema of the face abdominal wall or lower

extremities usually appears The skin becomes dry, and death occurs from cachexia or intercurrent disease

Diagnosis The clinical picture is not distinctive hence diagnosis depends upon recovery and identification of the adult worm passed in the feces or demonstration of the eggs in the stool

The adult may be confused with *Fasciola hepatica* and *Fasciola gigantica* from which it is distinguished by lack of a cephalic cone suckers of unequal size and unbranched intestinal crura

The eggs of *F buski* are large ranging between 130 and 140 μ in length by 80 to 85 μ in breadth They may be differentiated with difficulty from the eggs of *Fasciola hepatica* by means of the smaller operculum on the former *Eggs of F buski can usually be distinguished from* those of *Fasciola gigantica* as the eggs of the latter are longer ranging from 160 to 190 μ in length Most other operculate eggs found in the stool are smaller than those of *F buski*

Treatment The drug of choice in the treatment of fasciolopsiasis is Crystoids anthelmintic administered as for ascariasis A dose of 0 4 gram is given if the patient is under seven years of age 1 gram if older

Prophylaxis Prophylaxis is based upon two measures (*1*) *the* proper cooking of all roots and "nuts" which might serve as possible transfer agents" for *F buski* (2) education of foreigners to avoid sampling uncooked native dishes

Other measures include sufficiently prolonged storage of nightsoil to insure the destruction of eggs and the education of natives in the proper use and location of privies

Heterophyiasis

Definition Heterophyiasis is an infection by the minute intestinal fluke *Heterophyes heterophyes* (v Siebold 1852) Stiles and Hassall 1900 in the small intestine of man

Distribution It is common in the Nile Delta and in Japan southern Korea Formosa central and south China and the Philippines

Morphology The parasites are small spinose and *less than 2 mm*

' almost equal to and con

16 μ) eggs are operculate

icosa of the small intestine

where they may produce a mild irritation or a superficial necrosis of the mucosa Eggs may be deposited in the tissues and because of their minute size may be carried by *the blood stream to other areas* especially the brain the spinal cord and the heart muscle

Clinical Characteristics Symptoms include abdominal pain frequently associated with mucous diarrhea When eggs are distributed by the blood stream serious clinical disease may result with evidence of organic changes in the central nervous system and often cardiac insufficiency

Diagnosis *Diagnosis is based upon* the recovery from the stool of characteristic eggs which are difficult to differentiate from those *of other*

heterophyid trematodes (see p 518) They are small, operculate, ovoid, light brown in color and measure 29 by 16 μ

Transmission of the disease occurs through the eating of raw, or

A second species, *H katsuradai* (Ozaki and Asada, 1925), has been recovered from patients suffering from diarrhea in Japan The parasite is distinguished from *H heterophyes* by its relatively enormous acetabulum The eggs are slightly smaller, measuring 25 to 26 by 14 to 15 μ Transmission occurs by the eating of infected raw mullet flesh

A third species, *H brevicaeca* (Africa and Garcia, 1935), was reported from man in the Philippines In some cases heart lesions in man have been caused by the liberation of eggs of the heterophyids into the blood stream

Treatment. Tetrachloroethylene, as employed for hookworm is the drug of choice (see p 425), or treat as for fasciolopsiasis with Crystoids anthelmintic (see pp 414, 524)

Metagonimiasis

Metagonimiasis is due to the presence of a small trematode, *Metagonimus yokogawai* Katsurada 1912, attached to the intestinal mucosa of man Other animals, such as dogs, cats, pigs, mice and pelicans, may serve as reservoir hosts It is believed to be the most common heterophyid fluke of man in the Far East, being found in parts of China, Japan the Maritime Provinces of the U S S R and the northern provinces in Siberia It also occurs in man in Spain and various Balkan states The parasite is small, usually less than 3 mm in length, and resembles *H heterophyes* in size and shape, but differs in morphologic details Infection is acquired when the flesh of improperly cooked oriental fresh water trout or other fresh water fish is ingested The most common intermediate snail hosts of *Metagonimus* in the Orient are *Thiara granifera* (Lamarck) and *Semisulcospira libertina* (Gould)

Pathology. These flukes may actually invade the intestinal mucosa, producing inflammation and occasionally ulceration, they ultimately become encapsulated Rarely, eggs deposited in the tissues may be carried by the blood stream and deposited in other regions

Infection by this parasite usually causes few symptoms In heavy infections, however, especially when eggs have lodged in other tissues, serious disease may result The clinical picture in such instances will vary in accordance with the distribution and severity of the pathologic changes

Diagnosis. The diagnosis is based upon the recovery from feces of characteristic eggs, which resemble those of *Clonorchis sinensis* in shape but are almost indistinguishable from the eggs of *H heterophyes* They contain a fully developed embryo when passed in the stool and measure 26 5 to 28 0 μ by 15 5 to 17 μ

Treatment. Treat with tetrachloroethylene, as for hookworm (p 425) or with Crystoids anthelmintic (p 414)

Echinostomiasis

Echinostomiasis is a general term applied to infection by several related genera and species of spiny collared flukes which parasitize man Their distribution is limited to the Philippines Indonesia Assam and Japan

About ten species have been reported from man of which *Echinostoma ilocanum* from the Philippines and Java *E lindoensis* from Celebes and *Echinochasmus perfoliatus* from Japan are among the more important Although varying in size and morphologic details all members of the group are slender and flattened the majority being less than 25 mm long Identification is based on morphologic characteristics especially the size of the eggs and the arrangement and number of spines comprising the collar Infection is acquired by eating raw or improperly cooked fresh water snails and clams many of which serve as the second intermediate host these snails belong to such genera as *Pila Gyraulus Lymnaea* and *Thiara*

Pathology The echinostomes are found attached to the mucosa of the small intestine and their presence ordinarily does not appear to be associated with marked pathologic changes Heavy infections however may be accompanied by abdominal pain and diarrhea This infection has not been thoroughly studied

Diagnosis Diagnosis depends upon demonstration of the eggs in stools from the infected individual Echinostome infections may be differentiated from fascioliasis and fasciolopsiasis by the size of the egg since echinostomes have smaller eggs

Treatment. The following drugs have been recommended for the treatment of echinostomiasis oleoresin of aspidium for *E ilocanum* tetrachloroethylene for *E lindoensis* although no drug is known for *E perfoliatus* it appears probable that Crystoids anthelmintic would prove to be efficacious (p 414)

Gastrodiscıasis

Gastrodiscıasis is an infection by the trematode *Gastrodiscoides hominis* (Lewis and McConnel 1876) Fischoeder 1902 in the cecum and ascending colon of man It has been reported from man in Assam Cochin China and the U S S R The pig appears to be the common reservoir host

Diagnosis The parasite may be identified readily by its pyriform shape reddish orange color and the huge acetabulum which occupies the ventral posterior portion of the worm The acetabulum bears a characteristic notch at its posterior extremity Parasites range from 5 by 4 mm to 10 by 6 mm in size and have a conical anterior portion about 2 mm in length The eggs are ovoidal immature when passed and measure about 150 by 65 μ in length and breadth respectively

Clinical Characteristics Infection of man by this parasite is associated with diarrhea but other details of the clinical picture are unknown

Treatment Treat with tetrachloroethylene (p 425) or Crystoids anthelmintic (p 414)

Diseases Caused by Liver Flukes

Clonorchiasis

Synonym. Chinese liver fluke disease

Definition. Clonorchiasis is caused by the presence of the Oriental liver fluke, *Clonorchis sinensis*, in the biliary passages It may be associated with proliferation of the biliary epithelium, connective tissue hyperplasia and, in severe cases, fatty degeneration and cirrhosis of the liver

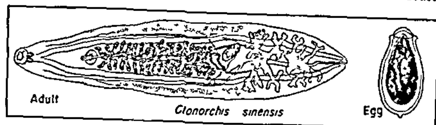
Distribution. This fluke occurs in the Far East as a common parasite of fish eating mammals The highly endemic regions of human infection are Japan Korea, China and Vietnam Clonorchiasis is especially important in Okayama Prefecture in Japan, South Korea, Kwangtung Province in South China and the Red River Delta in Tonkin Vietnam Infection by this parasite has also been recorded in Chinese inhabitants of the United States, Cuba and India and in native Hawaiians

Etiology. *Morphology* *Clonorchis sinensis* (Cobbold, 1875) Looss, 1907 is a slender, attenuated trematode ranging from 10 to 25 mm in length and 3 to 5 mm in breadth The oral sucker is clearly larger than the acetabulum Unstained specimens of *Clonorchis sinensis* placed between two slides and held to a strong light reveal the characteristic deeply lobulated testes lying in tandem in the posterior third of the worm Anterior to the testes is the ovarian complex, the uterine mass, typically appearing brown owing to the presence of numerous eggs, fills the middle third of the worm Laterally in the same region lie the vitellaria

Development The operculate eggs of *C sinensis* contain fully de [illegible] The eggs [illegible] The edge [illegible] which surrounds the lid this portion of the shell being markedly "shouldered" There is also a definite knob or boss at the anopercular end

The eggs, laid in the smaller bile passages, are carried down the common bile duct to the duodenum and pass in the stools The eggs must reach water and are believed to hatch when ingested by appropriate species of snails *Parafossarulus manchouricus* (= *P striatulus*), *Bulimus fuchsianus*, *Alocinma longicornis* (= *Bythinia longicornis*) and *Hua ningpoensis* Development within the snail requires four to five weeks and includes the production of mother sporocysts followed by a generation of rediae At the end of this interval typical lophocercous (tail with fin folds) cercariae break out of the rediae and emerge from the snail These cercariae penetrate beneath the scales and into the musculature of fresh water fish where, after a developmental period of several weeks, they produce cysts which are infective for the definitive host

After ingestion by man or other suitable mammalian hosts the cysts in the fish muscle are digested, and the contained parasites are released in the duodenum where they become attached to the mucosa They soon migrate to the smaller biliary radicles, especially those of the left lobe of the liver where they mature Experiments suggest that in experimental



CLONORCHIASIS

Infection of Reservoirs

Intermediate hosts

EPIDEMIOLOGY

1. Reservoir man, dog, cat
2. Intermediate hosts certain fresh-water snails & fish
3. Eggs from feces infect snail
4. Cercariae from snail infect fish
5. Metacercariae in muscles of fish
6. Raw fish ingested by man, dog, cat
7. Parasites localize in bile ducts

Fish metacercaria

Alocinma longicornis

Parafossarulus manchouricus

Snail hosts

Figure VII.81. Epidemiology of clonorchiasis

animals *Clonorchis* may reach the liver via the common bile duct or by a more circuitous migration through the peritoneal cavity The entire cycle requires approximately three months

Epidemiology. *Clonorchis sinensis* is found principally in the bile passages of dogs, cats and man, although other fish eating mammals may be infected The infective or metacercarial stage occurs in the mus

culture of over 40 species of fresh water fish belonging to the Cyprinidae, Gobiidae, Anabantidae and Salmonidae Fish ponds or canals in China are often the chief source of human infection These pondlike areas are filled with water much of the time and consequently afford ideal habitats for snails and fish serving as intermediate hosts for this parasite Man acquires the infection from the ingestion of raw, inadequately cooked, or even dried, salted or pickled flesh of infected fresh water fish (Fig VII 81)

It appears likely that Hawaiians become infected through shipments of infected frozen dried or pickled fish from China or Japan

Pathology. Adult *C sinensis* tend to localize in the distal bile passages, especially those of the left lobe of the liver One result of infection is proliferation, sometimes desquamation of the biliary epithelium while in the larger ducts progressive dilatation thickening of the wall and crypt formation occur It is believed by some workers that toxic secretions of the parasite may be responsible for some of the pathologic changes which are found in ducts too small for the worm to penetrate Liver damage however, depends upon the number of parasites present the age of the infection and the number of reinfections that have occurred In endemic areas surprisingly large numbers of parasites have been found at autopsy, as many as 21,000 having been recovered from a single individual

varying

nchyma

r of the

lobule are not unusual Even in light infections significant histologic changes are usually present in the liver (Fig VII 82)



Figure VII.82 *Clonorchis sinensis* in dilated biliary duct adult with eggs in uterus

Clinical Characteristics Three typical stages in the development of clonorchiasis are recognized (1) Early manifestations of the disease are fever eosinophilia leukocytosis and epigastric pain (2) The second stage is characterized by diarrhea and progressive hepatomegaly and rarely prolonged low grade fever episodes of jaundice and tenderness over the liver also may be present (3) The most advanced cases are associated with cirrhosis of the liver ascites anasarca cachexia and occasionally extreme jaundice

It should be borne in mind however that in endemic areas the majority of infected individuals harbor few worms and do not show significant symptoms

Prognosis is good in cases of light infections Patients rarely die from this disease alone death however may occur in heavy infections of long standing when the parasites have caused serious impairment of liver function

Diagnosis Diagnosis depends upon the detection of the characteristic eggs in the feces or in bile or fluid obtained by a duodenal intubation Differentiation from eggs of closely related heterophyid flukes especially those of *Metagonimus yokogawai* and *H heterophyes* is necessary Eggs of *M yokogawai* are yellowish in color and lighter than those of *H heterophyes* the lighter color being due to the thinner shell The eggs of *C sinensis* become narrower toward the operculate end and the shell is more distinctly "shouldered" where the operculum occurs (Fig VII 78 p 518) Eggs of *Opisthorchis felineus* are elongate ovoidal and about three times as long as broad Adults must be distinguished from the broader heavier more ovate members of the *Fasciola* group

At autopsy the bile ducts should be examined carefully for the presence of this and other parasites of the biliary passages and liver proper

Treatment Treatment is unsatisfactory Chloroquine diphosphate (Aralen) is beneficial or curative in some cases The dosage of Aralen employed is 0 5 gram twice daily for three days followed by 0 5 gram once a day for
orally in 1½ l
with meals for
in advanced cases

Prophylaxis The prevention of clonorchiasis in persons residing in an endemic area can be accomplished effectively by insistence upon the thorough cooking of all fresh water fish Foreigners should be discouraged from sampling native dishes Other measures include the storage and treatment of nightsoil with ammonium sulfate and the education of the population to use privies

Opisthorchiasis

This disease is due to the presence of the trematode *Opisthorchis felineus* (Rivolta 1884) Blanchard 1895 or *O viverrini* (Poirier 1886)
r

frequently in cats and
the common trematode
infection of man in Prussia and in parts of Siberia It also has been

reported from man in India, Japan and Vietnam and is believed to be present in other areas of the Far East *Opisthorchis viverrini* appears to be the dominant liver fluke of man in parts of Thailand

Etiology. *Morphology* *Opisthorchis felineus* resembles *O viverrini* and *C sinensis* in general shape and arrangement of the organ systems It is a slender worm 7 to 12 mm in length and 2 to 3 mm in breadth, tapering anteriorly and rounded posteriorly The oral sucker and acetabulum are about of equal size (250 μ), whereas in *C sinensis* the oral sucker is the larger In *O felineus* the testes are lobate and arranged obliquely, in *C sinensis* they are more deeply lobed and are arranged in tandem The small, elongate, ovoidal eggs are roughly three times as long as broad (about 30 by 11 μ) and contain a miracidium when the egg is laid The operculum fits into a thickened rim of the shell, eggs may be distinguished from those of *C sinensis* by their smaller diameter and less pronounced shouldering at the margin of the operculum Adult specimens of *O viverrini* resemble those of *O felineus* in morphology, however, the eggs of *O viverrini* average 26 7 by 15 μ and resemble those of *C sinensis* more than those of *O felineus*

The eggs of *O felineus* are believed to be ingested by the snail *Bulimus tentaculatus*, where they hatch and develop, producing lophocercous cercariae in about two months These penetrate several fresh water cyprinoid fish, which after a suitable developmental period for the metacercariae are infective for man and other hosts when their raw infected flesh is ingested It appears on epidemiologic grounds that the cycle of *O viverrini* is similar to that described for *O felineus*

Pathology and Clinical Aspects The pathology and clinical aspects of opisthorchiasis are not thoroughly understood, although in general they resemble those of clonorchiasis The degree of damage to the liver and bile ducts depends upon the mass and duration of the infection Local injury may be expected in the distal bile capillaries and surrounding liver tissue when large numbers (several hundred) are present In severe infections and in heavy and long continued reinfection, painful enlargement of the liver, jaundice and congestion of the spleen are not uncommon In such cases invasion of the pancreas may occur

Treatment. Similar to that of clonorchiasis Chloroquine diphosphate has significant anthelmintic activity against *O viverrini* and presumably against related species (se page 530)

Fascioliasis

Synonyms. Fascioliasis hepatica "liver rot," or sheep liver fluke disease

Definition. Fascioliasis is a disease caused by the presence of the sheep liver fluke *Fasciola hepatica*, in the bile ducts or liver parenchyma The disease is characterized by hyperplasia of the biliary epithelium, dilatation of biliary passages, leukocytic infiltration and periductal fibrosis It is essentially a disease of sheep in which it produces "liver rot" Man is occasionally infected

Table VII.12. Distribution of Fascioliasis in Man by Countries

Africa Algeria French Somaliland	Europe Corsica France Hungary Italy Rumania Salonika USSR Scotland	South America Argentina Chile Uruguay Venezuela
Asia China Turkestan		West Indies Cuba Puerto Rico
Asia Minor Syria Turkey (especially near the Dardanelles)		
Australia Queensland		

Distribution. *Fasciola hepatica* is widely distributed in sheep throughout the world wherever the proper snail host is present (see Table VII 12)

Etiology. *Morphology* *Fasciola hepatica* Linnaeus, 1758, is a large, brownish, flat fluke about 25 mm in length and 13 mm in breadth The integument of the anterior portion of the worm is covered with scalelike spines A cephalic cone extends 4 to 5 mm anteriorly beyond the ovoid body proper Oral and ventral suckers 1 and 1 6 mm in diameter lie at the distal and basal portions of the cone, respectively Posteriorly this parasite is broadly pointed Nearly all organs, especially the testes, vitellaria, ovary and the two main intestinal crura are highly branched and widely distributed throughout the parenchyma In adult specimens the uterus, which is confined to the anterior third of the worm is filled with large operculate eggs usually a light brown color, ranging between 130 and 150 μ in length and 63 to 90 μ in breadth, they are undeveloped when deposited

Development The eggs, which must reach water after leaving the host, require a developmental period of nine to 15 days Undeveloped eggs remain viable in moist feces up to nine months Upon hatching the miracidia may penetrate many different species of snails where each parasite becomes a mother sporocyst The next generations are known as rediae and daughter rediae, respectively The latter produce free living cercariae which emerge from the snail about 30 days after penetration by the miracidium and encyst upon aquatic vegetation or debris, or even free in shallow water, until they become metacercariae In the absence of freezing or desiccation, the cysts remain viable for months

Upon ingestion by the final host the parasites excyst in the intestine and migrate through the intestinal wall Some reach the liver by the hepatic portal circulation, others pass into the peritoneal cavity and penetrate the liver capsule, ultimately reaching the bile ducts where they mature Adult parasites have survived three years in rabbits and at least five years in sheep

Epidemiology. Numerous ruminants especially sheep, goats, cattle, horses and camels, as well as some carnivores, such as dogs, may

harbor the adult *F hepatica* Numerous snails including species of *Lymnaea* of the subgenera *Pseudosuccinae* and *Fossaria,* also the genera *Bulimus, Succinea, Praticolella* and *Pomacea* serve as intermediate molluscan hosts The infective, or metacercarial, stage is so readily acquired in endemic areas through the ingestion of vegetation, such as water cress and possibly water containing the cysts, that infections of many host species including man occur

Fascioliasis is geographically widespread The parasite does not require large bodies of water for its development Consequently pasture lands with small or temporary ponds and sluggish brooks are a frequent source of infection Three factors are concerned primarily in the epidemiology of fascioliasis (1) Many different species of snails may serve as the initial host (2) Almost any green vegetation furnishes the necessary surface upon which the cercariae may encyst (3) The feeding proclivities of sheep and cattle make them ideal reservoir hosts

Pathology. Infection of sheep by *F hepatica* is characterized by extensive liver damage Fascioliasis of man is usually a mild disease although in the rare case of heavy infection the biliary passages are the site of hyperplasia, necrosis and cystic dilatation accompanied by leukocytic infiltration Also, on rare occasions the adult worms may occlude the common bile duct The young larvae usually enter the liver from the peritoneal cavity by penetration of the capsule In subsequent migrations they destroy liver parenchyma and produce more or less extensive necrosis and fibrosis In very heavy infections the parasites



Figure VII 83 *Fasciola hepatica* in biliary duct—not marked proliferation of bile epithelium.

Clinical Characteristics. The symptoms include vomiting cough ing and generalized abdominal pain Occasionally jaundice urticaria, diarrhea and irregular fever are present A pharyngeal type of fascioliasis (halzoun) is known among the peoples of Lebanon owing to the ingestion of infected raw livers of goats and sheep In such cases the worms often are lodged on the mucosa of the pharynx These exotic infections result in dyspnea dysphagia or deafness

Diagnosis Diagnosis depends upon finding the large operculate eggs 130 to 150 μ in length in the feces or in material obtained by duodenal or biliary drainage False diagnoses may be made in areas where infected livers are eaten raw In such instances eggs from these livers appear in the stools after passing through the intestinal tract A differential diagnosis can be made by placing the patient on a liver free diet for a few days If eggs continue to be passed the infection is genuine

Infections by *F hepatica* must be differentiated from those caused by other worms (both liver and intestinal) as well as other liver ailments accompanied by jaundice and hepatomegaly Eosinophilia is suggestive

The liver and its ducts should be examined carefully at postmortem for the presence of this and other liver inhabiting parasites

Treatment Intramuscular injections of emetine hydrochloride have been recommended in fascioliasis A dose of one half grain (0 03 gram) for adults daily for 18 days may be of clinical benefit or even curative

Prophylaxis Drainage of pastures and perhaps the elimination of the snail host through the use of derris copper sulfate or some other molluscicides may control this disease in limited areas In endemic rural areas the use of water cress should be avoided In regions where sheep livers are eaten they should be thoroughly cooked before being con sumed

Fascioliasis Gigantica

Fascioliasis gigantica is due to the presence of the giant liver fluke *Fasciola gigantica* Cobbold 1856 in the liver tissues and ducts of man Human infections have been reported occasionally from Africa and Asia The fluke is more lanceolate and has a shorter cephalic cone a larger acetabulum and a more anterior location of the testes than *F hepatica* The eggs range from 160 to 190 μ in length and 70 to 90 μ in breadth The biologic and pathologic picture is similar to that described for *F hepatica* Treat as for *F hepatica* infections

Dicrocoeliasis

Dicrocoeliasis is due to the presence of *Dicrocoelium dendriticum* (Rudolphi 1818) Looss 1899 in the biliary passages of man a condition which may be confused with fascioliasis The small fully embryonated eggs are 38 to 45 μ in length by 22 to 30 μ in breadth They are ingested by various species of land snails in which the eggs hatch and develop Cercariae are released from the snail in slime balls these are eaten by ants in which the cercariae develop into metacercariae The parasites mature following ingestion of the ant by herbivorous definitive hosts

Infections in man while recorded in Europe North Africa U S S R China and Syria are not commonly encountered No treatment appears to be satisfactory It is suggested that this infection be treated as for *C sinensis* (see p 530)

Diseases Caused by Lung Flukes

Paragonimiasis

Synonyms Pulmonary distomiasis endemic hemoptysis oriental lung fluke disease

Definition Paragonimiasis is a disease of man caused by the presence of the oriental lung fluke *Paragonimus westermani* encapsulated in the parenchyma of the lung

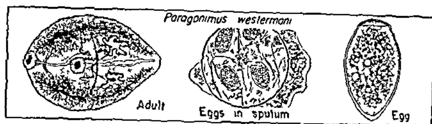
Distribution *Paragonimus westermani* is widely distributed being especially prevalent in the Far East The distribution of the disease is summarized in Table VII 13 which also lists the important foci of human infection

Etiology *Morphology* *Paragonimus westermani* (Kerbert 1878) Braun 1899 is a plump ovoid fluke lacking definitely attenuated extremities In life it is reddish brown in color and 8 to 20 mm in length by 5 to 9 mm in breadth *Microscopic scalelike integumental* spines are present The two approximately equal well defined suckers are about 0 8 mm in diameter the ventral or acetabular sucker lying just anterior to the equatorial plane on the ventral surface Stained specimens reveal the irregularly lobed testes situated side by side in the posterior half of the body The long slender excretory bladder extends from the posterior tip to the region of the pharynx In carefully flattened preserved and stained specimens the eccentric centrally located lobate ovary can be seen to one side of the acetabulum At the lateral margins extending from the oral sucker to the posterior tip are the yolk glands

Table VII 13 Distribution of Paragonimiasis by Countries

Africa	Far East	India
Belgian Congo	*Central China	Assam
British Cameroons	Vietnam	Bengal
French West Africa	*Japan	Malabar
Tripoli	*Korea	Madras Presidency
	Manchuria	
	*Formosa	**South America**
	Samoan Islands	Brazil (Matto Grosso area)
	Malay Peninsula	Peru
	*Philippines	Ecuador
	Indonesia	Venezuela
	New Guinea	

* Indicates important endemic foci in man



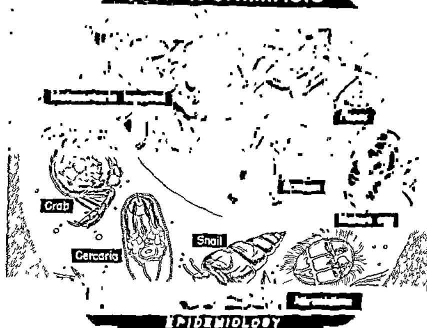


Figure VII 84. Epidemiology of paragonimiasis

the uterus occupies the central portion of the worm opposite the ovary Anteriorly are the globose pharynx and a short esophagus which divides to form the two unbranched intestinal crura (VII 84)

A closely related species, *P ohirai*, has been reported from Japan, *P kellicotti* has been described from North American mammals Opinion is still divided as to the synonymy of *P kellicotti* with *P. westermani*

Development The mature adults produce eggs which range between 80 and 118 μ in length by 48 and 60 μ in width averaging 85 by 53 μ These eggs are slightly broader at the operculate end and show some shouldering where the operculum originates Posteriorly the shell is thicker than in the anterior half The undeveloped eggs are passed up the respiratory tree and either expectorated in the sputum or swallowed and passed in the feces Under satisfactory conditions they hatch in water after 17 to 21 days liberating characteristic miracidia These penetrate various species of snails The most important species are *Semisulcospira libertina* (Gould) *S amurensis* (Gerstfeldt) and its subspecies *gottschei* (von Martens) and *nodiperda* (von Martens) *Thiara (Tarebia) granifera* (Lamarck) and *Hua toucheana* (Heude) *Paragonimus* has also been recorded in *Oncomelania nosophora* (Robson) and *Syncera lutea* (A Adams) (= *Assiminea*) *Pomacea luteostoma* needs confirmation as the host in Venezuela *Pomatiopsis lapidaria* is the known host for the so called *P kellicotti* of North America

Three to five months are required to produce the successive generations of mother sporocyst rediae and finally the stumpy tailed or microcercous cercariae within the tissues of the snail

The cercariae attack crayfish and fresh water crabs the second intermediate host invading the muscles and viscera where they become metacercariae infective for man after a developmental period of several weeks The following crustaceans serve as hosts for the metacercariae of *P westermani* in the Orient *Cambaroides japonicus C similis Eriocheir japonicus E sinensis Potamon (Geothelphusa) dehaani Potamon (Potamon) rathbuni P (P) denticulatus Parathelphusa sinensis Sesarma (Holometopus) dehaani Sesarma (Sesarma) intermedia* (=*S* (*S*) *sinensis*) In Venezeula the cercariae encyst in *Pseudothelphusa iturbe* and *P kellicotti* in North America encysts in members of the genus *Cambarus*

Infection of man and other reservoir hosts results when the crustacea containing metacercariae of *P westernmani* are eaten raw The metacercariae excyst in the duodenum and migrate through the wall of the alimentary canal into the peritoneal cavity Most migrate through the diaphragm and penetrate into the parenchyma of the lungs where the parasites are finally encapsulated by the host About three weeks are needed for this migration even though the diaphragm may be reached in three to four days Maturity is attained five to six weeks after ingestion

Epidemiology The following includes some of the carnivores and omnivores in addition to man which serve as reservoir hosts for species of *Paragonimus* tiger cat wild cat leopard fox wolf dog panther rat(?) hog beaver wolverine civet cat (*Viverra zibetha ashtoni*) Chinese lesser civet cat (*Viverricula malaccensis pallida*) pencilled cat (*Nyctereutes procyonides*) mongoose (*Herpestes urva*) and Indian mongoose (*Mungos mungo*) (see Table XII 10 p 520) All acquire the metacercariae through the ingestion of infected raw fresh water crabs or crayfish In addition man secures the infection by eating salted or wine soaked parasitized crustacea While the wine kills the crabs the metacercariae survive for several hours (Fig XII 84)



Figure VII 85 *Paragonimus westermani in the lung of a bengal tiger* (Courtesy of Dr T W M. Cameron Macdonald College of McGill University)

The disease is limited to areas where such dishes are common or where crabs are eaten raw roasting or heating the crustacea in water at 55° C for five minutes will kill the metacercariae thus preventing infection

Pollution of water by the eggs of the parasites especially those from reservoir hosts other than man serves as the principal source of infection for the snails which in turn produce the cercariae that invade the crustacean hosts

Pathology The young flukes migrate through the peritoneal cavity and penetrate the diaphragm to reach the lungs Many never reach their destination but become encapsulated and sometimes destroyed in other locations Parasites encysted in the intestinal mucosa elicit an inflammatory reaction which sometimes terminates in ulceration resulting in passage of eggs in the feces

The *most characteristic and significant pathologic changes are found* in the lungs (Fig VII 85) These have been divided by some into four categories as follows (1) nonsuppurative with eggs infiltrated in host tissue leading to round cell and connective tissue reaction and usually to abscess formation (2) tubercle like in which the abscess may contain caseous material (3) suppurative and (4) ulcerative in which healing is only partially successful

On arrival in the pulmonary tissue the parasites produce a surrounding inflammatory reaction with leukocytic infiltration necrosis of parenchyma and the formation of an enclosing fibrous tissue capsule The resulting cysts which may reach 2 cm in diameter are more frequent in the deeper portions than at the periphery of the lung In other instances

tunnels or burrows lined with fibrous tissue are formed from damaged and dilated bronchioles and bronchi and larger cysts may be formed by break down of adjacent tunnel walls The lesions are often directly connected with radicles of the bronchial tree

The cysts characteristically have a reddish or chocolate brown color while the cystlike burrows often have a bluish tint Each cyst contains one or more living or dead worms together with quantities of brownish necrotic frequently purulent exudate composed of eggs debris and Charcot Leyden crystals (Fig VII 86)

Leukocytosis with eosinophilia may occur but is frequently absent In highly endemic areas such as parts of Korea and Japan cerebral para gonimiasis with its attendant complications is fairly common

Clinical Characteristics. The clinical picture of paragonimiasis is predominantly that of a chronic bronchitis or bronchiectasis with morn ing cough productive of variable amounts of gelatinous tenacious sputum which characteristically is brownish or reddish in color Exertional dyspnea is common The term endemic hemoptysis is due to the frequency with which hemoptysis occurs When cysts are localized in close proximity to the pleura pleural pain may be troublesome or pleural effusion may occur In other instances the clinical phenomena indicate a nonresolving bronchopneumonia In heavy infections lung abscess may occur

Abdominal symptoms occur when considerable numbers of parasites have localized in this region They include pain tenderness rarely muscle spasm and diarrhea that is sometimes bloody with mucus and eggs in the stools

The cerebral type of the disease occurs only when wandering parasites

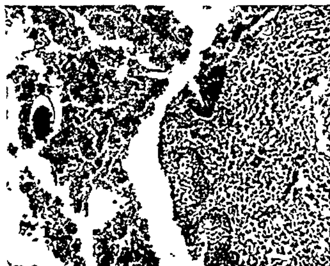


Figure VII.86 Egg of *P kellicotti* in exudate in bronchus

lodge in the brain The local lesions in these cases resemble those of cysticercosis, and epilepsy is a frequent clinical manifestation

Rarely, localization in the skin or subcutaneous tissues leads to abscess formation

The prognosis is good in light infections, in heavy infections, however, it is grave

Diagnosis. The clinical picture of pulmonary paragonimiasis and especially the brownish or reddish purulent sputum may be suggestive

A positive diagnosis is made by detecting the characteristic eggs in the sputum, feces and more rarely, the cutaneous lesions By using the AMS III technique (acid–sodium sulfate–Triton–ether) on stool specimens nearly 80 per cent of a known positive series were positive by stool (see page 810 for details of technique) While this egg is sometimes confused with that of the fish tapeworm, a careful comparison of the two makes differentiation possible The sputum may contain egg masses that appear as rusty brown flecks, or it may be tinged with blood Leukocytes, especially eosinophils and Charcot-Leyden crystals also appear in the sputum (See page 818 for details of technique for examining sputum)

It is necessary to differentiate paragonimiasis from such other pulmonary diseases as lobular pneumonia, tuberculosis, bronchial spirochetosis and bronchiectasis

The abdominal form of the disease may be confused with a variety of intestinal infections, new growth, and certain surgical lesions The cerebral type likewise may produce a varied clinical picture These unusual localizations seldom permit etiologic diagnosis from the clinical findings Intradermal tests, using antigen made from adult worms (1 10000) gave 90 to 95 per cent correlation with known positives in Japan

Treatment. No satisfactory treatment is known Emetine hydrochloride given intramuscularly or subcutaneously seems to be the drug of choice (see page 287 for dosage) The emetine may be supplemented concurrently with 0 5 gram of sulfadiazine four times daily for ten days Some cases respond well to this therapy, after one or two courses symptoms and eggs disappear and relapses do not occur However, in most cases the effect is mainly symptomatic and temporary Patients who are not cured by one or two courses of emetine usually do not respond to subsequent courses of the same drug The administration of chloroquine phosphate over long periods (see page 530 for dosage) in some cases results in clinical improvement and reduction or disappearance of eggs from the sputum and stool

Prophylaxis. Human infection may be avoided easily by thorough cooking of all fresh water crustaceans used for food The relatively large number of reservoir and intermediate hosts in many endemic areas renders effective control by other measures impracticable or impossible at present

52

Cestodes

Introduction

Biology of the Cestodes

The cestodes or tapeworms include several divergent groups which may be separated not only morphologically but also on clear cut biologic criteria The latter distinctions become evident as the life cycles of the parasites are studied Biologic criteria also modify the various epidemiologic patterns On such criteria the cestodes may be divided into two large groups In the first the eggs must reach water, in the second this is not necessary. The broad tapeworm of man *Diphyllobothrium latum* is the only important human parasite in the first group * All the remaining common tapeworms of man fall in the second category One cestode of man *Hymenolepis nana* requires no intermediate host but passes directly from person to person Other species must have at least one intermediate host to complete the cycle Although the members of these two groups will not be segregated as their morphology is discussed their biology is sufficiently distinct to warrant separate consideration of their development (Fig VII 87)

Morphology of the Cestodes

The Adults. The tapeworms Cestoda or cestodes as they are commonly called range in size from the small *Hymenolepis nana* of 40 mm or less to the huge *Taenia saginata* and *Diphyllobothrium latum* which may measure up to 10 or 12 meters in length Members of this entire class have morphologic and biologic characteristics which differentiate them from the other helminths

All tapeworms have a mechanism for attaching the *scolex* or "head to the host s intestinal wall In the case of *Diphyllobothrium latum* and related species the scolex bears two sucking grooves or *bothria* which serve in this capacity Other common human tapeworms possess four round and highly muscular sucking cups located on the scolex These in turn may be supplemented further by a terminal sometimes retractile protuberance known as a *rostellum* The rostellum in a given species of tapeworm is characteristic and is often armed with small hooks the

* The eggs of *Diplogonoporus grandis* are not considered here as only a few cases of human infection are known

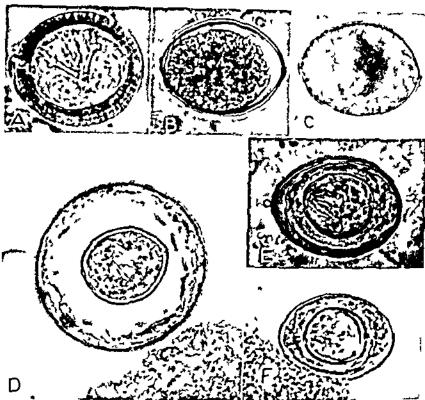


Figure VII 87 Some cestode eggs A Human tapeworm *Taenia* sp 750× B Broad tapeworm of man *Diphyllobothrium latum* 500× C Broad tapeworm of man *Diphyllobothrium latum* 500× D Rat tapeworm *Hymenolepis diminuta* 650× E Dwarf tapeworm *Hymenolepis nana* 750× F Dwarl tapeworm *Hymenolepis nana* (note polar filaments 750× (Figs B and F courtesy of Lt L. W Shatterly School of Aviation Medicine Gunter AFB Alabama all others courtesy of Dr R. L. Roudabush. Ward s Natural Science Establishment Rochester New York photos by T Romaniak)

number, the length and the arrangement of which serve as further differential aids (Fig VII 88)

Behind the scolex is a short, unsegmented narrow neck which is the region from which the partially segmented young *proglottids* develop This region of immature proglottid formation is succeeded by a region
ment
ıtıd
ıch
exclusive of the scolex, represent the oldest portion of the worm As new segments are continuously being formed at the neck the old proglottids are pushed farther and farther from the scolex, thereby increasing the length of the parasite The entire worm from the scolex to, and including the gravid proglottids is termed the *strobila*

Tapeworms differ from most other helminths in that they have no alimentary canal Each mature proglottid possesses nerve trunks, ex cretory canals a well developed musculature and a complete set of male

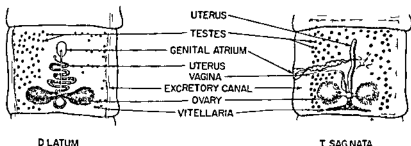
SCOLICES







MATURE PROGLOTTIDS



GRAVID PROGLOTTIDS

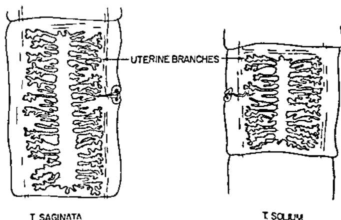


Figure VII 88 Scolices and proglottids of some tapeworms of man. The full complement of testes and vitellaria is not shown. (Modified from various authors courtesy of University of Florida College of Medicine)

tiated, operculate eggs of parasites in this category develop in water hatch, and liberate a free swimming ciliated larva or *coracidium* This organism is ingested by a copepod (a minute crustacean), the first intermediate host, and metamorphoses into a procercoid larva The next intermediate host is a fish, in which the plerocercoid stage, infective for man, develops Infection occurs when insufficiently cooked fish containing this parasite is eaten

Embryonated Eggs. All the human tapeworms considered in this category retain the eggs in utero until they are embryonated, at which time the six hooklets, diagnostic of such tapeworm eggs become apparent These worms may require an intermediate host for the completion of development In the case of *Hymenolepis nana* none is necessary as infection is direct—the only requirement being the introduction of viable eggs into a susceptible definitive host Eggs of the others after reaching the ground, are ingested by the intermediate host where development to the infective stage, usually a cysticercoid, cysticercus or hydatid cyst, takes place When these larvae in the infective stage are ingested by man or other final hosts, the parasites reach maturity in the digestive tract

Diphyllobothriasis

Synonyms. Broad tapeworm infection fish tapeworm infection

Definition. Diphyllobothriasis is the infection of man by adult *Diphyllobothrium latum* Its presence is sometimes associated with debility, anemia and loss of weight

Distribution. *Diphyllobothrium latum* is common in persons living in the Baltic countries, the western U S S R, Finland parts of Scandinavia and in certain endemic foci in the United States and Canada In the latter regions the parasite occurs in northern Wisconsin Minnesota Michigan and in provinces of Canada bordering on those states In these populations the prevalence varies between 2 and, rarely, almost 100 per cent A few cases have been reported also from Florida The parasite occurs in the lake regions of Italy, Switzerland parts of Germany, and in the valley of the Danube, particularly in Rumania It has been reported in Manchuria Japan portions of Siberia and in scattered areas of Africa It is also indigenous to Chile, Argentina and Australia

Etiology. *Morphology* The broad tapeworm of man *D latum* (Linnaeus 1758) Luhe 1910 lives with its scolex attached to the mucosa of the small intestine It may reach a length of 10 meters or more The spatulate head is small and bears a deep sucking groove on either surface Posterior to the scolex is the narrow unsegmented neck 5 to 10 mm in length, the remainder of the worm consists of 3000 or more segments or proglottids

The chief diagnostic feature of *D latum* is the rosette-shaped egg

filled uterus of the gravid proglottids The finding of the genital pore on the flattened surface in the anterior third of the proglottid is also helpful Gravid segments are normally retained as part of the strobila ... een estimated that ... eggs a day These ... ntode eggs have a lid or operculum they are undeveloped when laid

Development The eggs must reach water where after approximately two weeks at the optimum temperature the egg hatches liberating a free swimming coracidium consisting of a typical six hooked onchosphere invested by ciliated epithelium The larva must be ingested by species of *Cyclops* or *Diaptomus* (copepods) About eight species are believed to act as hosts for this tapeworm Within the alimentary tract the larva loses its ciliated epithelial layer and immediately penetrates to the body cavity of the copepod where it develops into a procercoid larva in ten to 20 days The cycle is continued when the infected copepod is ingested by any of 22 or more species of fresh water fish capable of serving as the second intermediate host The larva migrates from the alimentary canal to the flesh where it coils between the muscle fibers as a plerocercoid often reaching a length of 16 mm or more It becomes infective in one to four weeks the time varying with the temperature It is believed that often two fish one of which becomes infected by eating the other may serve as intermediate hosts When a viable parasite is ingested by man the larva develops to maturity in the intestine The complete cycle requires eight to 15 weeks

Epidemiology In the United States the wall-eyed pike sandpike great northern pike and burbot have been implicated as second intermediate hosts In Africa it is the barbel in Europe the pike perch salmon Millers thumb trout lake trout grayling white fish ruff and eel are known hosts Comparable species of trout or salmon serve in Japan Transmission of the parasite to man is accomplished by the eating of insufficiently cooked fish containing viable plerocercoid larvae House wives who sample ludefisk" or "gefullte" fish while it is being prepared are often infected as well as persons eating the fish (Fig VII 92)

It is believed by many that bears mink foxes cats mongooses walruses seals sea lions pigs and dogs serve as reservoirs in endemic areas

Pathology In most infections with *D latum* there is scant evidence of significant pathologic change The presence of the adult worms in the intestine causes no distinct lesions Occasionally infection with *D latum* is productive of anemia

Clinical Characteristics Infection with *D latum* is asymptomatic in many people Others however experience abdominal pain excessive appetite and may suffer a loss of weight

The anemia which occurs in some persons with *D latum* infection is megaloblastic and clinically resembles genuine pernicious anemia The fish tapeworm has been found to contain considerable amounts of vitamin B_1 and competes with the host for this metabolite If the parasite is located in the proximal portion of the jejunum manifest B_1- deficiency

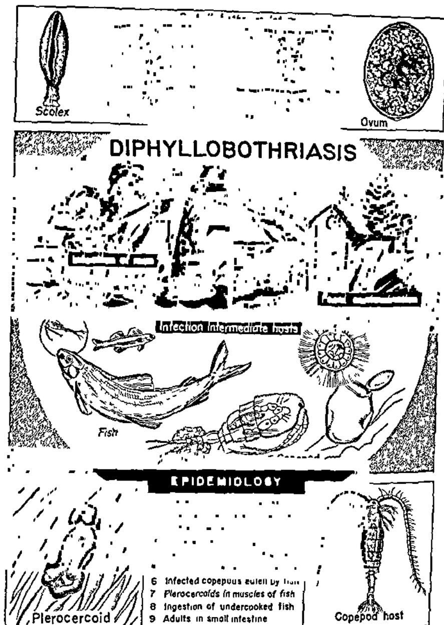


Figure VII 92. Epidemiology of diphyllobothriasis

(pernicious anemia) may develop The absorption of this vitamin also is disturbed in nonanemic carriers of the worm.

Diagnosis. Diagnosis depends upon the recovery of the characteristic op- ... eggs in the stool These must be differentiated from eggs of ot... *...ni,* *occurring* ... *rus*

grandis which has been reported only from the Japanese Diagnosis may be confirmed following the administration of a saline purge which usually results in the recovery of some proglottids of the worm These should be examined to determine the arrangement of the reproductive system since the rosette shaped uterus lying medially in each proglottid is diagnostic while there is a bilateral set in *D grandis*

Treatment The accepted anthelmintic for intestinal tapeworm infection is quinacrine hydrochloride (Atabrine) (see pages 557–558) The administration of folic acid for the anemia should supplement anthelmintic therapy

Prophylaxis The prevention of *D latum* infection is readily accomplished by thorough cooking of fish before consumption Freezing the fish for 24 to 48 hours at 14° F (−10° C) will also effectively destroy the plerocercoid larvae Other measures which might be practiced under favorable conditions include sewage treatment in endemic areas and the education of Scandinavian and Jewish housewives against sampling "ludefisk" and "gefullte" fish while preparing it

Sparganosis

Synonym Sparganum infection

Definition Sparganosis is caused by the presence of migrating larvae or spargana of several species of tapeworms related to *D latum* but requiring final hosts other than man Localization occurs primarily in the subcutaneous tissue and muscle fascia

Distribution The greatest number of cases of sparganosis has been reported from Japan Korea China Vietnam and Indonesia scattered instances are known from other areas of the world including Holland British Guiana Uruguay and the United States

Etiology Sparganosis is a disease caused by the migration of several species of closely allied parasites which accidentally infect man These parasites normally mature in other mammals such as dogs and cats Morphologically indistinguishable spargana occur in subcutaneous tissue and between the muscles of frogs snakes birds and mammals in endemic areas It has been shown in the case of *Diphyllobothrium mansonoides* that the eggs hatch in water and the coracidium is ingested by a copepod Following ingestion of the infected copepod spargana develop in mice and rhesus monkeys whereas adult worms mature in the definitive or final hosts the dog cat or bobcat (Fig VII 93) Most cases of sparganosis in the United States probably are caused by this species

Sparganum proliferum (Ijima 1905) Stiles 1908 is a proliferating larva which is unknown in the adult stage In the tissues of man it appears as an elongate mass with branched and sometimes proliferating processes Some of these may become separated from the parent worm

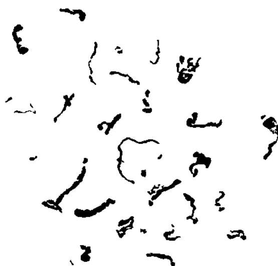


Figure VII 93 *Sparganum proliferum* excised larvae (Courtesy of Dr J F Mueller Syracuse University Medical School)

and develop individually These parasites invade not only the subcutaneous tissues and intermuscular fasciae but also the viscera and brain

Epidemiology. Human sparganosis results from either of two causes (1) the ingestion of infected copepods containing the infective larvae, or (2) the local application of infected vertebrates to the skin as poultices from which the larvae migrate into human tissue

Pathology. The larvae invade primarily the subcutaneous tissues where they develop and produce considerable inflammation, swelling and fibrosis When opened the lesions may be characterized by a slimy matrix within which the living larvae contract and elongate Sometimes the parasite has degenerated and only a caseous mass remains (Fig VII 94)

In China, where infections occur in the eye owing to the application of infected frogs as poultices, edematous conjunctivitis and corneal ulceration are seen

Clinical Characteristics. Symptoms depend upon the number of larvae present and their location Many cases of light infection remain asymptomatic Infected cutaneous tissues become edematous and extremely painful to the touch Lesions of the skin also may reveal acne like nodular pustules frequently surrounded by tissue honeycombed with parasites Ocular sparganosis results in redness, nodule formation, edema in the conjunctiva, excessive lachrymation, toxemia and, in cases of penetration of the retrobulbar region corneal ulceration

Diagnosis. Infections due to sparganosis are extremely difficult to diagnose except in areas where they are common Consequently they often remain undiagnosed until after surgical removal of the worm



Figure VII.94 Sparganosis larva of *D phyllobothrium mansonoides* in tissues showing surrounding inflammation and foreign body reaction (Courtesy of Dr J F Mueller Syracuse University Medical School.)

Treatment The lesion may be injected with 2 to 4 ml of 40 per cent ethyl alcohol with Novocain (epinephrine free) to kill the worms in situ thus permitting ultimate resorption Other workers recommend 0 3 to 0 45 gram per dose of novarsenobenzol intravenously for adults This drug is given every four to five days for two to six administrations In some instances excision may prove more satisfactory

Prophylaxis Infection by this parasite can be avoided in endemic areas by the use of boiled or adequately filtered water Education of the public against the application of freshly killed vertebrates as poultices is essential if ultimate control is to be achieved

Taeniasis Solium

Synonyms Pork tapeworm infection *Taenia solium* infection cysticercosis

Definition Taeniasis solium is due to the presence of the adult pork tapeworm *T solium* in the intestine of man cysticercosis is caused by the cysticerci in the tissues of man

Distribution The pork tapeworm has a cosmopolitan distribution being found throughout the world wherever raw or inadequately cooked

pork is eaten Infection is rare in England Canada and the United States In Mexico and parts of Central and South America the infection rate is somewhat higher In Europe, the Slavic groups are most heavily infected in the U S S R the rates vary from 0 2 to 1 5 per cent

Etiology. *Morphology* The adult "measly pork" tapeworm *Taenia solium* Linnaeus 1758 attains a length of 2 to 7 meters It lives attached to the intestinal wall of man The scolex is about 1 mm in diameter and has been described as being "roughly quadrate" Anterior and central to the four suckers is a prominent terminal rostellum which bears two circular rows of hooklets These hooklets number between 22 and 32 in an upper and lower row The neck is short Posterior to this structure are the immature mature and gravid proglottids The mature proglottids are nearly square and although the gravid ones are longer than broad they do not attain the length of the corresponding proglottids of *T saginata* Morphologically the mature proglottids of *T solium* are in general similar to those of *T saginata* except that the testes in the former number between 150 to 200 compared with the 300 to 400 in *T saginata* In addition the ovary is trilobed instead of bilobed as in *T saginata* The uterine sac runs up the middle of the proglottid with the ovarian complex in the posterior third of the segment In the more elongate gravid proglottids the reproductive organs degenerate with the exception of the uterus which has seven to 13 (an average of nine) main lateral branches on a side

Eggs are spherical to subspherical in shape 31 to 43 μ in greatest diameter and cannot be differentiated from those of *T saginata* The terminal proglottids often become separated and are passed entire Occasionally they migrate actively from the anus when the host is not at stool

Development The eggs burst from the gravid proglottids either before or after the proglottids have become detached from the strobila Eggs reaching the soil remain viable for weeks and when ingested by hogs or man hatch immediately The liberated oncosphere penetrates the intestinal wall and reaches the lymphatic or circulatory system These embryos are distributed throughout the body most localizing in the musculature or subcutaneous tissues Within 60 to 70 days they become metamorphosed into infective bladder worms or *Cysticercus cellulosae* about 5 mm in length by 8 to 10 mm in breadth

In the usual course of events cysticerci reach man when he ingests raw or inadequately prepared measly pork The larvae are digested out of the cysts became attached to the intestinal wall and grow to maturity in five to 12 weeks *Taenia solium* adults are believed to have survived as long as 25 years in the intestine of man

Epidemiology Man is the only known definitive host of *T solium* and the hog is the usual intermediate host Two forms of human infection occur When man serves as the definitive host the adult tapeworm is present in the intestine Such infection is acquired only by the ingestion of raw or insufficiently cooked "measly pork containing viable cysticerci (Fig VII 95)

In cysticercosis man serves as the intermediate host and the larval

stages cysticerci are present in his tissues Human infection results usually from the ingestion and subsequent hatching of viable eggs They reach the alimentary canal in food or drink contaminated by feces from a person harboring the adult worm Autoinfection may occur when eggs are carried from feces to the mouth on the hands of infected persons It is believed to occur also when reverse peristalsis brings egg laden pro-

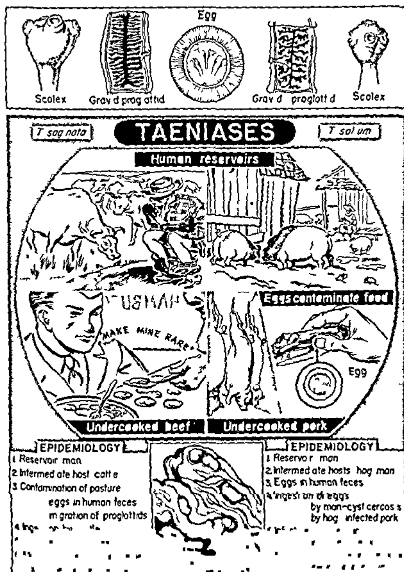


Figure VII.85 Epidemiology of the taeniases

glottids back to the stomach or duodenum where they hatch Occasionally other primates dogs and sheep are infected with cysticerci

Taeniasis solium infection with the adult worm is not found among such groups as the Jews and Mohammedans since they rarely eat pork cysticercosis on the other hand may occur

The infection is maintained in nature by improper disposal of human feces which permits ingestion of the eggs by the normal intermediate host the hog

Pathology *The Adult Worm* The mature tapeworm in the intestine seldom causes significant pathologic changes A moderate eosinophilia may be present

Cysticercus Cellulosae The cysticerci may be lodged in any tissue of the body They are most frequently found in the subcutaneous tissues brain eye skeletal musculature heart liver lungs and abdominal cavity The larvae cause at first a local surrounding inflammatory reaction with infiltration by neutrophils eosinophils and lymphocytes and a stimulation of fibroblast production Subsequently the larvae become enclosed within a fibrous capsule or necrosis may occur followed by caseation or calcification Giant cells may be found about the lesions The resulting cysts may vary from 0 5 to 2 or even 3 cm in diameter

Clinical Characteristics *The Adult Worm* Common complaints include passing of "segments" abdominal or epigastric pain increased appetite hunger pains weakness and weight loss

Cysticercus Cellulosae The clinical picture of cysticercosis is extremely variable and depends upon the location and the number of cysticerci in the host When these are few and restricted principally to the subcutaneous tissues symptoms may be negligible or absent When they localize in the brain the spinal cord the eye or the heart muscle serious effects are common The phenomena associated with tumor formation in the particular anatomic region are then noted Localization in the fourth ventricle or in the cerebral cortex is frequent and in these instances there may be epileptiform convulsions mental changes and other phenomena which accompany brain tumors irrespective of type (Fig VII 96) Eosinophilia is not remarkable in this infection

Cysts may be palpable as firm nodules in the superficial tissues

Diagnosis *The Adult* Differentiation between *T saginata* and *T solium* infections on the basis of their eggs is not possible Therefore it is important to differentiate between the mature proglottids which may be pressed between two slides and held to the light The uterus may be injected with India ink to facilitate the determination of the number of main lateral uterine branches which range between seven and 13 in *T solium*

Cysticercus Cellulosae The occurrence of epilepsy or the clinical picture of brain tumor developing in a previously healthy individual who is known to have been in a hyperendemic area should arouse suspicion and lead to careful search of the entire body surface for the characteristic nodules in the subcutaneous tissues Soft tissue roentgen examination of the extremities will often reveal characteristic "rice grain" or puffed rice calcific shadows

The differential white blood count is not of assistance in view of the frequent lack of eosinophilia Precipitin tests are only group specific and not generally available Definitive diagnosis depends upon recovery of the larva by excision of a cyst and identification of species by the presence of two rows of hooks of unequal size on the inverted rostellum

Since cysticercosis may be due to autoinfection stool examinations should be made for the presence of eggs in the event intestinal infection is still present A history of tapeworm infection should be sought

Treatment. Quinacrine hydrochloride (Atabrine) is quite efficacious (see page 557) Since Atabrine may induce emesis drugs which depress the vomiting center may be of value in treating for *T solium* infection

There is no specific treatment for cysticercosis Individual cysts which are causing pressure symptoms may be amenable to surgical excision

Prophylaxis Intestinal infection by *T solium* is prevented by proper cooking of all pork products Cysticerci present in pickled or salted pork may be viable they are destroyed however by freezing *United States Government meat inspection provides a safeguard but not* complete protection

Sanitary disposal of human feces prevents infection of the hog and is the essential procedure in the control of taeniasis solium

Cysticercosis may often be prevented by prompt and effective therapy of the individual harboring the adult worm efficient methods of personal cleanliness to prevent autoinfection and protection of food and drink against possible contamination by human feces containing eggs of *T solium*



Figure VII 96 Cysticercus of *T solium* in brain Note slight tissue reaction of host, rostellar hooks and laterally placed suckers of parasite

Synonyms Beef tapeworm infection *Taenia saginata* infection

Definition Taeniasis saginata is caused by the presence of the adult beef tapeworm *T saginata* in the intestine of man

Distribution The beef tapeworm is cosmopolitan in distribution

Etiology *Morphology* *Taenia saginata Goeze 1782* is a large tapeworm usually 5 to 10 meters in length The scolex appears quadrate in cross section and carries four round suckers The rostellum and hooks typical of *T solium* are lacking in *T saginata* The neck is short being about half as broad as the head and several times its length Then follow the immature mature and gravid proglottids respectively The mature proglottids are broader than long and contain about twice as many testes (300 to 400) as comparable proglottids of *T solium* The gravid proglottids are longer than broad 5 to 7 mm in width by about 20 mm in length There are 15 to 20 main uterine branches on either side of this median saclike structure which virtually fill the entire proglottid

The spherical to ovoid eggs are 31 to 43 μ in greatest diameter and cannot be differentiated from the eggs of *T solium* The oncosphere containing six characteristic hooklets is surrounded by a narrow space filled with a transparent material This clear area in turn is surrounded by a thick outer shell heavily marked by radial striations The delicate hyaline thin outer envelopes which surround these eggs in utero are rarely present when the eggs are detected in the stool

Development Eggs develop in cattle giraffes llamas and buffaloes Sheep and other herbivorous animals are recorded as experimental intermediate hosts After ingestion the outer shell membrane is digested thus setting the embryos free in the upper part of the small intestine These larvae migrate through the intestinal wall of the intermediate host reach the blood or lymph streams and are carried about the body until filtered out in the striated muscles Here they metamorphose into cysticerci Man the only definitive host acquires the infection upon ingesting infected meat containing viable *Cysticercus bovis* An incubation period of eight to 12 weeks is required for maturation of the parasite and the appearance of eggs in the stool

Epidemiology Infectı

or poorly cooked beef (Fig

such as the Mohammedans

of beef before eating it thı

United States only about 0 37 per cent of the federally inspected cattle has been found infected Soil may be contaminated directly by eggs in feces or indirectly by viable proglottids Even when the infected individual is not at stool the latter sometimes migrate through the anus and subsequently reach the ground

Pathology No significant pathologic phenomena usually occur although detached proglottids occasionally migrate to the appendix and through occlusive or traumatic actions initiate appendicitis Eosinophils

may be moderately or, occasionally markedly increased Human infection with *Cysticercus bovis* is very rare

Clinical Characteristics Many cases of taeniasis saginata are asymptomatic Patients with beef tapeworm infection usually give a history of passing proglottids Although many infected persons exhibit no symptoms a significant percentage of cases may have abdominal or epigastric pain increased appetite weakness or malaise and weight loss Vertigo nausea vomiting dyspnea headache and diarrhea are among the infrequent manifestations in cases of taeniasis saginata

Diagnosis Diagnosis depends upon (1) the detection of characteristic *Taenia* like eggs in the stool and (2) the finding of gravid proglottids since species identification cannot be made from eggs alone The proglottids may be pressed between two glass slides and the number of main lateral uterine branches counted under a dissecting microscope or with a hand lens These range in number from 15 to 20 and average 18 or 19 on each side In *Taenia solium* there are only seven to 13 with an average of nine on each side

Treatment. Quinacrine hydrochloride (Atabrine) is the drug of choice It has largely replaced oleoresin of aspidium Hexylresorcinol administered by duodenal intubation gives good results but is an inconvenient method of treatment Di Phenthane 70 a veterinary product has been shown to be effective in eliminating *Taenia saginata* and *T solium* from man A preparation containing a mixture of metallic tin stannous oxide and stannous chloride is reported to be nontoxic and to provide good therapeutic results in human taeniasis but it is not generally available

The following method of administration of quinacrine hydrochloride usually is effective in removing *T saginata* *T solium* and *D latum* Nausea vomiting and abdominal cramping frequently occur The diet on the day before treatment should be bland or liquid A saline purge is given in the afternoon No food is permitted on the morning of treatment until a bowel movement is obtained after therapy On the morning of treatment a saline cleansing enema is given One hour after the enema two 0 1 gram tablets of quinacrine hydrochloride are taken every five minutes with a little water until the total dosage is consumed The dosage for adults is 1 0 gram It should be reduced for smaller persons and children according to size and age If the tablets of quinacrine are vomited the lost dosage may be repeated after the vomiting has ceased The addition of sodium bicarbonate to the water taken with the drug may obviate or minimize the reactions in patients who do not tolerate quinacrine well Two to four hours after administration of the drug the purge is repeated It is important that the post treatment purgative should be sufficient to produce a copious evacuation The desired dosage can usually be determined on the basis of the results of the cathartic given on the day prior to treatment All stools passed within 24 hours after treatment should be examined carefully for the minute scolex Inability to demonstrate the scolex is not necessarily an indication of failure of treatment Repetition of therapy is not indicated until evidence of infection such as proglottids or eggs in the stool reappears These signs may

not appear until several weeks after unsuccessful *treatment If only a* small portion of the tapeworm is passed stool examination may be made at weekly intervals in an effort to demonstrate eggs of the tapeworms In case of complete failure treatment may be repeated safely after an interval of one week

Prophylaxis Beef tapeworm infections may be prevented in the United States by avoiding all beef that does not bear a proper inspection label Adequate freezing or salting of uninspected meat is efficacious The eating of raw beef should be discouraged Thorough cooking of beef prevents infection of man and the sanitary disposal of human feces prevents infection of the intermediate host

Unilocular Hydatid Disease

Synonyms Echinococciasis echinococcosis echinococcus disease

Definition This is an infection by the larval form of *Echinococcus granulosus* [illegible] the formation [illegible] in character [illegible] *coccus multilocularis (see page 563)*

Distribution Unilocular hydatid disease is prevalent in sheep raising countries *where man is closely associated with* heavily *infected* sheep dogs Such regions are mainly temperate or subtropical Table VII 14 shows the distribution of hydatid disease by continents and countries

Etiology *The Adult* Adult *Echinococcus granulosus* (Batsch 1786) Rudolphi 1805 (= *Taenia echinococcus*) occur mainly in carnivores such as dogs wolves jackals and cats These are small tapeworms ranging from 1 5 to 6 mm in length and consisting of four parts (1) The pyriform scolex is only about 0 3 mm in diameter and carries four suckers and a rostellum which bears two circular rows of hooklets varying in total number but ranging from 28 to 50 (usually 30 to 36) The scolex is continued without evidence of segmentation into a narrow neck (2) Behind this occurs an immature proglottid (3) More posteriorly is the single mature proglottid which is nearly twice as long as the preceding one and which contains a complete set of reproductive organs (4) The terminal or gravid proglottid may reach 2 mm in length It consists principally of a uterus with lateral evaginations *these become so* distended with eggs that the uterus finally bursts liberating the eggs *either before or after detachment from the strobila* The eggs are indistinguishable from other *Taenia* eggs found in dogs or man They possess *thick brown shells which surround* the six hooked oncospheres Maximum diameter of the eggs is 30 to 38 μ

The Larva Human infection results from the ingestion of the eggs of *E granulosus* These hatch in the duodenum and most of the liberated oncospheres then penetrate its wall The larvae are carried

Table VII 14 Distribution of Hydatid Disease

Africa	Asia	Australasia
*Algeria	*Palestine and Syria	*South Australia
Tunisia	North China	*Tasmania
Liberia	Mongolia	*New Zealand
*Egypt	Japan	Europe
Abyssin a	Tonkin	*Central
*Cape Colony	Philippine Islands	Northern
*Tanganyika	S beria	North America
	Arabia	U S (occasional)
	Ind a (Punjab area)	Canada
		Alaska
		South America
		*Argent na
		Chile
		*Uruguay
		*Paraguay

* Regions of h gher incidence in man

throughout the body most being filtered out in the liver and lungs and the remainder in other tissues where many of them are destroyed by phagocytic cells Probably 60 to 70 per cent of the surviving larvae reach maturity in the liver Growth at first takes place quite rapidly on the fourth day the parasite is only 40 μ in length but in three weeks it is 0 25 mm long At the end of five months it has grown to about a centi meter in size Cysts subsequently grow more slowly and frequently come to the notice of a physician as late as 20 years after the initial infection

If a young developing unilocular cyst is comparatively uninfluenced by pressure the following structural characteristics of the growth may be noted

(1) An external laminated cuticula

(2) An interior germinative membrane which buds off the daughter cysts or brood capsules

(3) The hydatid fluid which fills the hydatid cysts and gradually pro duces considerable distention

(4) The germinative membrane which lines the new budding daughter cysts

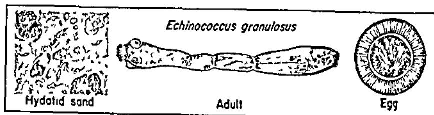
(5) The daughter cysts free in the hydatid fluid which in turn may produce granddaughter cysts within them

(6) Some of the brood capsules become separated from the wall and ettle to the bottom together with liberated scolices as a fine "hydatid and"

Not all of the germinal epithelium that lines the hydatid cyst is fertile r are all the daughter cysts fertile

The cycle in nature is completed when the hydatid cysts are ingested ally by a carnivore as for example when a sheep dog feeds on the arded viscera of a slaughtered infected sheep or a wolf preys upon ock The hydatid cyst contains many scolices each of which may de p to a mature adult tapeworm in the intestine of the carnivorous host

idemiology Hydatid disease is important in many parts of the d The dog is the common definit... nd the chief reservoir of





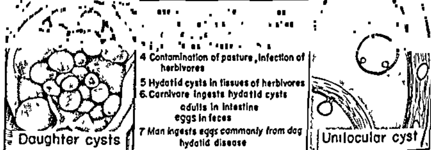


Figure VII 97. Epidemiology of unilocular hydatid disease

infection, although other wild CANIDAE have been reported as carrying the adult

casionally

adult para

grazing over this seeded area ingest the eggs After a variable period these intermediate hosts develop characteristic hydatid cysts, the scolices

of which will produce adults when they are ingested by a suitable definitive host Human infection results from ingestion of eggs of *Echinococ-*

picion, since many carry the adult tapeworms Dogs in Iceland formerly were heavily infected (28 per cent), and human infections ran as high

3 per cent of the human population is infected In New Zealand about 120 human cases with about 14 per cent fatality are seen each year

In northern Canada "sylvatic echinococciasis" exists Wolves are highly infected and seed areas with eggs These are ingested by such wild herbivores as the caribou and moose, and the cycle is completed when these herbivores are killed by wolves This sylvatic cycle enters the domestic picture because the wild herbivores are slaughtered in large numbers for food The viscera are fed to the dogs, which become infected with the adult parasite By infecting his dogs man initiates a cycle in which he may assume the role of intermediate host, and so eventually develops echinococciasis

Pathology. The unilocular hydatid cyst produces a characteristic reaction on the part of the host This consists at first of a localized surrounding inflammatory reaction with infiltration by eosinophils, round cells and giant cells This is followed by fibroblast proliferation and the gradual formation of an enclosing fibrous capsule As progressive growth of the cyst takes place pressure necrosis of adjacent tissue occurs (Fig VII 98, VII 99)

Hydatid cysts may develop in bone causing extensive destruction, and spontaneous fractures and non-union are not unusual The subse-



Figure VII.98 Unilocular hydatid cyst of liver containing daughter cysts.

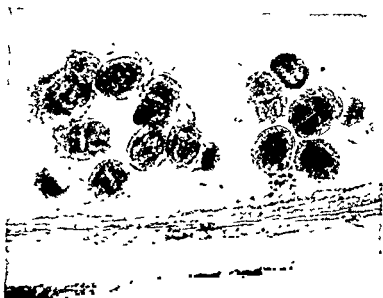


Figure VII 99. Wall of hydatid cyst two daughter cysts budding from germinal epithelium of wall Note contained scolices (Courtesy Dr A C. Chandler Rice Institute)

quent invasion of the soft tissues is typically associated with the deposition of calcium

Since the oncospheres are distributed through the body by the blood stream, hydatid cysts may develop in any region They are most commonly found, however, in the liver, lungs, omentum and mesentery

Clinical Characteristics. Hydatid cysts frequently cause no symptoms during early stages, especially if localized in the liver but later as the tumor increases in size it may give rise to both subjective and objective signs due to pressure Most patients with unilocular hydatid disease have complaints referable to the biliary tract or complaints such as bloating, indigestion nausea and vomiting Histories of mild pain in the right upper abdominal quadrant, severe biliary colic and of jaundice during the attacks of pain are relatively common Cysts frequently rupture and discharge their contents into a large bile duct The resulting embolic obstruction of the biliary tract accounts for the colicky pain and jaundice Unilocular cysts may suppurate and produce a clinical picture of hepatic abscess Hydatid cysts may rupture into the peritoneal cavity, lung, pleura, bronchus and kidney Release of hydatid fluid may produce a severe and even fatal reaction

When the cyst is located in bone, spontaneous fracture and deformity may result, if the brain is the site of the infection, epilepsy and blindness may become apparent In about 12 per cent of the cases the lungs may be involved Such cases are characterized by cough, hemoptysis and sometimes fever

Diagnosis. A history of signs indicative of an expanding tumor in an individual who has been in an endemic area may be suggestive

Eosinophilia however occurs in only 20 to 25 per cent of the cases Hydatid thrill may be demonstrable over large intra abdominal cysts when present it is a specific diagnostic sign of unilocular hydatid Roentgen examination may likewise be of assistance the cysts frequently have a cannon ball shape If cysts of the lung have ruptured into a bronchus examination of the sputum may reveal hydatid sand Exploratory puncture is not advised because of the hazard of anaphylactoid reaction and of contaminating uninjured tissues

Intradermal precipitin and complement fixation tests are reasonably specific and valuable diagnostic aids Obviously stool examination is of no value in human hydatid disease

Treatment The only effective treatment is complete excision of the cyst Whether this is practical depends upon the location and type of cyst Surgical intervention should be considered only in cases of unilocular cysts In many cases the cyst may be removed intact but such a procedure is difficult as the fibrous capsule surrounding the cyst proper gradually gives way to normal tissue Two procedures have been commonly used (1) Aspiration of 10 to 15 ml of the fluid and replacement with 10 per cent formalin This kills the scolices and brood capsules and renders the contents of the cyst harmless in the event they are accidentally scattered during removal (2) Marsupialization in which case the cyst after sterilization with 10 per cent formalin may be stitched to the abdominal wall and allowed to heal by granulation Since hydatid fluid may be released or spilled during the operation patients may be protected from allergic or anaphylactic reaction by administration of adrenocortical steroids during and after operation

Prophylaxis Prophylaxis of the disease on a wide scale entails elimination of the infection in the common definitive host Deworming of dogs with arecoline hydrobromide is practiced in some heavily endemic areas Proper disposal of carcasses on sheep ranges or of entrails leaving slaughter houses will prevent dogs from gaining access to them Prophylaxis so far as sporadic human cases are concerned involves caution against the contamination of hands food or drink with dog feces

Alveolar Hydatid Disease

Definition. This infection is caused by larval stages of *Echinococcus multilocularis* (Leuckart 1863) Vogel 1955 These invade the affected organs and destroy the host s tissues The parasites behave very much as an infiltrating neoplasm

Distribution. *Echinococcus multilocularis* is known to occur in south central Europe mainly in the neighborhood of the Alps throughout much of the Soviet Union and in northern and western Alaska It has also

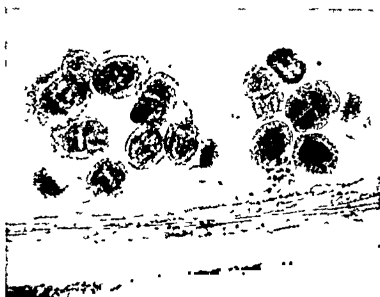


Figure VII 99 Wall of hydatid cyst two daughter cysts budding from germinal epithelium of wall Note contained scolices (Courtesy Dr A C Chandler Rice Institute)

quent invasion of the soft tissues is typically associated with the deposition of calcium

Since the oncospheres are distributed through the body by the blood stream hydatid cysts may develop in any region They are most commonly found, however, in the liver, lungs, omentum and mesentery

Clinical Characteristics. Hydatid cysts frequently cause no symptoms during early stages, especially if localized in the liver, but later as the tumor increases in size it may give rise to both subjective and objective signs due to pressure Most patients with unilocular hydatid disease have complaints referable to the biliary tract or complaints such as bloating indigestion nausea and vomiting Histories of mild pain in the right upper abdominal quadrant, severe biliary colic and of jaundice during the attacks of pain are relatively common Cysts frequently rupture and discharge their contents into a large bile duct The resulting embolic obstruction of the biliary tract accounts for the colicky pain and jaundice Unilocular cysts may suppurate and produce a clinical picture ... peritoneal cavity

... biliary
...dness
...ay be
some-

times fever

Diagnosis. A history of signs indicative of an expanding tumor in an individual who has been in an endemic area may be suggestive

Eosinophilia however, occurs in only 20 to 25 per cent of the cases Hydatid thrill may be demonstrable over large intra abdominal cysts when present it is a specific diagnostic sign of unilocular hydatid Roentgen examination may likewise be of assistance the cysts frequently have a cannon ball shape If cysts of the lung have ruptured into a bronchus examination of the sputum may reveal hydatid sand Exploratory puncture is not advised because of the hazard of anaphylactoid reaction and of contaminating uninjured tissues

Intradermal precipitin and complement fixation tests are reasonably specific and valuable diagnostic aids Obviously stool examination is of no value in human hydatid disease

Treatment. The only effective treatment is complete excision of the cyst Whether this is practical depends upon the location and type of cyst Surgical intervention should be considered only in cases of unilocular cysts In many cases the cyst may be removed intact but such a procedure is difficult as the fibrous capsule surrounding the cyst proper gradually gives way to normal tissue Two procedures have been commonly used (1) Aspiration of 10 to 15 ml of the fluid and replacement with 10 per cent formalin This kills the scolices and brood capsules and renders the contents of the cyst harmless in the event they are accidentally scattered during removal (2) Marsupialization in which case the cyst after sterilization with 10 per cent formalin may be stitched to the abdominal wall and allowed to heal by granulation Since hydatid fluid may be released or spilled during the operation patients may be protected from allergic or anaphylactic reaction by administration of adrenocortical steroids during and after operation

Prophylaxis. Prophylaxis of the disease on a wide scale entails elimination of the infection in the common definitive host Deworming of dogs with arecoline hydrobromide is practiced in some heavily endemic areas Proper disposal of carcasses on sheep ranges or of entrails leaving slaughter houses will prevent dogs from gaining access to them Prophylaxis so far as sporadic human cases are concerned involves caution against the contamination of hands food or drink with dog feces

Alveolar Hydatid Disease

Definition This infection is caused by larval stages of *Echinococcus multilocularis* (Leuckart 1863) Vogel 1955 These invade the affected organs and destroy the host s tissues The parasites behave very much as an infiltrating neoplasm

Distribution. *Echinococcus multilocularis* is known to occur in south central Europe mainly in the neighborhood of the Alps throughout much of the Soviet Union and in northern and western Alaska It has also

been found on Nunivak and St Lawrence Islands (Alaska) and has been introduced on Bering Island in the Middle Kuriles and on Rebun Island (Japan)

Etiology. *The Adult* Foxes are the important hosts of the adult worms in nature, but dogs and cats also become infected The strobila consists of a scolex, neck and single immature, mature, and gravid pro-

no lateral branches, the genital pore of the gravid segment is located near the middle, and the testes are distributed from the level of the genital pore to the posterior end of the segment The number of testes ranges from 17 to 26 and averages 22 In contrast, lateral branches of the uterus are present in *E granulosus*, the genital pore is near the posterior end of the segment, and the testes are located both anterior and posterior to the genital pore, the testes range from 45 to 65, with an average of 56

The Larva Unlike *E granulosus* which produces large single cysts with endogenous growth and a well defined fibrous tissue encapsulation *E multilocularis* forms an aggregate of innumerable small cysts These proliferate by exogenous budding The alveolar hydatid in human tissue appears as small, irregular cavities with thin and crumpled hyaline membranes In some human infections the parasites are sterile and no scolices are present in the alveolar cavities As the cysts develop, particularly in animal hosts, numerous calcareous bodies appear throughout the germinal membrane The number of brood capsules and scolices then increases filling the many alveolar cavities

Epidemiology. The natural intermediate hosts of *E multilocularis* are field mice and other small mammals These herbivorous animals, and occasionally man, become infected by swallowing eggs from the feces of the carnivorous definitive hosts The latter in turn are infected through preying upon microtine rodents such as field mice, and ingesting the scolices contained in their larval cysts In boreal regions sledge dogs are the usual source of human infection, although foxes may be important under some conditions In agricultural regions man may acquire the infection by consuming fruits and vegetables contaminated by the excreta of foxes or other canids, by handling contaminated soil, picking and eating berries grown close to the soil, and through association with infected dogs and cats Children may acquire the infection by eating or soiling their hands with dirt in areas frequented by dogs, cats, wolves and foxes

Pathology. The liver is involved in over 90 per cent of human infections Larval growth is exogenous and a progressive invasion of the infected organ results, owing to the lack of a circumscribing capsule The tissue is honeycombed by the alveolar hydatid When the tumor has grown sufficiently, it begins to break down in the center, forming an abscess like cavity while the peripheral cysts continue to multiply (Fig VII 100) The parasite resembles a malignant tumor in its behavior, even to the point of forming metastases

Clinical Characteristics The disease runs a chronic afebrile course characterized by hepatomegaly and later by splenomegaly icterus and ascites *The clinical signs are typical of intrahepatic portal tension*

Diagnosis The differential diagnosis between alveolar echinococcosis and carcinoma of the liver is very difficult clinically As a rule the diagnosis is established by histologic examination of biopsy specimens The Casoni intradermal test and the complement fixation test with ordinary hydatid antigen are not always reliable Preliminary serologic studies suggest the possibility of using the bentonite flocculation test as an aid in the laboratory diagnosis of this infection

Treatment. This consists of surgical extirpation of the involved portion of the organ However early diagnosis is difficult and advanced cases usually are inoperable Radiation therapy has not been of significant value

Prophylaxis. Prevention includes control of dogs and cats measures to avoid fecal contamination of food and water supplies by dogs and other hosts of the adult worms and careful handling of wild canids such as foxes



Figure VII 100 Alveolar hydatid cyst invading liver (From Faust and Russell Clinical Parasitology Philadelphia Lea & Febiger 1957)

Other Tapeworms Infecting Man

There are records in the literature of infection of man by many other tapeworms A few of these parasites are discussed briefly in the following paragraphs

Hymenolepiasis Nana

Synonym Dwarf tapeworm infection

Definition Hymenolepiasis nana is caused by the presence of *Hymenolepis nana* in the alimentary canal of man

Distribution This small tapeworm has a cosmopolitan distribution It is known to occur most frequently in temperate and tropical climates

Etiology *Morphology* *Hymenolepis nana* (v Siebold 1852) Blanchard 1891 is 25 to 40 mm in length by 1 mm in breadth The scolex bears four small suckers and a short rostellum armed with 20 to 30 hooks arranged in a single ring The rostellum and the hooks may be invaginated into the tip of the scolex

Development This tapeworm requires no intermediate host Eggs are infective for man and mice Hatching occurs in the small intestine where each oncosphere penetrates a villus and develops into a cysticercoid Eventually the minute parasites break out into the lumen of the gut pass further down the tract and attach themselves between the villi where they reach maturity Internal autoinfection may occur and probably accounts for persistent heavy infections There is experimental evi



Figure VII.101 Cyst cercoid of *H nana* in intestinal villus of mouse (Courtesy Dr Arne V Hunninen)

dence which indicates that fleas and beetles (*Tenebrio*) and other insects may serve as nonobligatory intermediate hosts (Fig VII 101)

Epidemiology The worm is especially prevalent in children In fection is acquired initially by ingestion of the infective eggs passed in the stools The murine strain may be acquired by children however the important reservoir is the human one

Pathology There are no characteristic pathologic changes A mod erate eosinophilia sometimes accompanies a heavy infection

Clinical Characteristics Patients infected by these parasites are usually asymptomatic except when worms are present in large numbers In such cases abdominal pain and diarrhea may occur

Diagnosis Diagnosis is based upon the following characteristics of the eggs (Fig VII 87) (1) shape—usually ovoid (2) size—30 to 47 μ in diameter (3) shell—hyaline with clear area between shell and inner envelope (4) six hooked embryo—enclosed in an inner envelope (5) filaments—four to eight threadlike filament the two polar thick

Treatm Crys toids anth it is usually necessary to repeat treatment e or more times at intervals of two weeks to obtain a cure Therapeutic results obtained with Atabrine in dosages similar to those employed for malaria (p 340) for giardiasis p 293) or for large tape worm (p 557) occasionally eliminates *H nana* infections which are re fractory to other therapy The infection usually does not justify use of rigorous therapeutic measures and excessive purgation should be avoided in children

Prophylaxis. Prophylaxis depends upon sanitary disposal of human feces Domestic rodent control and proper protection of food will prevent infection originating from mice

Hymenolepiasis Diminuta

Synonym. Rat tapeworm infection

Definition. Hymenolepiasis diminuta is due to the presence of *Hymenolepis diminuta* in the alimentary canal of man

Distribution T

parasite of rats and

siding in the U S S ates (especially Georgia Tennessee and Texas) India Italy and Japan

Etiology *Morphology* The rat tapeworm *Hymenolepis dimin uta* (Rudolphi 1819) Blanchard 1891 ranges from 20 to 60 cm in length The scolex carries four suckers and an unarmed retractile rostel lum *Mature proglottids are wider than long* each contains a central ovary flanked on one side by two testes and on the other side by one Eggs are nearly spherical measuring 60 to 86 μ in greatest diameter The yellowish outer membrane is distinct and is clearly set off from the inner membrane which invests the six hooked oncosphere The space between the outer and inner membranes is filled with a gelatinous sub stance

Development Since the gravid proglottids disintegrate after detachment from the strobila eggs appear in the feces of the definitive host Numerous insects such as fleas cockroaches and meal worms may ingest the eggs and serve as intermediate hosts for this tapeworm These animals become infective for the final hosts as soon as the cysticercoid larvae have completed their intermediate development

Epidemiology Infection in man occurs through the ingestion of parasitized insect hosts which are often encountered in grains and cereals In many instances the pa
the insect from the larval
cannot feed on solids afte

Pathology No pathologic changes are recognized

Clinical Characteristics The alleged symptoms include indefinite gastrointestinal complaints diarrhea and abdominal pain



Figure VII 102 *Hymenolepis diminuta attached to intestinal mucosa of rat*

Diagnosis Diagnosis depends upon detecting eggs with the following characteristics (Figs VII 87 VII 88) (1) shape—roughly spherical (2) size—moderately large 60 to 86 μ (3) shell—transparent yellowish outer membrane lines shell clear area between this zone and the thick inner envelope (4) six hooked onchosphere—within inner envelope the latter sometimes bearing polar thickenings but never polar filaments

Treatment Same as for hymenolepiasis nana (see page 557)

Prophylaxis The ingestion of infected insects especially those occurring in processed grains and cereals to which rodents have access should be guarded against Education and provision for adequate sanitation with reference to rodent control and food storage are important preventive measures

Dipylidiasis

Dipylidium caninum (Linnaeus 1758) Railliet 1892 is a common tapeworm of dogs and cats throughout the world It has been found infrequently in humans in the United States Argentina Guatemala most European countries the Philippine Islands China and Southern Rhodesia Eggs from feces or from disintegrated proglottids in soil may be ingested by larval fleas and develop ultimately into infective cysticercoid larvae These larvae remain viable while the fleas metamorphose to the adult stage Infection in dogs and cats is due to the ingestion of infected fleas and possibly lice which serve as intermediate hosts Human infections occur primarily in children The insects may gain access to their mouths when they fondle pets

Diagnosis The gravid proglottids are shaped like melon seeds and are characterized by having a genital pore on each side Single or multiple segments of the parasite may be passed in the stool or may migrate from the bowel The eggs are in packets several eggs are encased in a capsule The spherical capsule is red which accounts for the pink tinge of the gravid proglottids

Clinical Characteristics Treatment and Prophylaxis Essentially the symptoms and therapy of *D caninum* infection are similar to those of *H nana* and *H diminuta* infections (see page 567 for treatment) Dusting dogs and cats with DDT to eliminate their ectoparasites will help prevent human infection and reinfection of the pets

VIII

Nutritional Diseases

Frederick J Stare and Jean Mayer

53

Introduction

The science of nutrition is concerned with food and the ingredients of food necessary for health, with the physiologic action of these nutrients and with the consequences of lack of effective concentrations of the 50 or 60 known specific substances The same essentials are provided by many different staples It is possible therefore, to provide protective diets by utilizing a variety of foods In fact, variety of diet constitutes one of the cardinal principles of nutrition practice Except in the case of milk for infants there is no single food which, of itself, is essential for good nutrition, and even in this instance a "soybean milk" provides a satisfactory substitute

An adequate diet must contain sufficient amounts of protein fat, carbohydrate, water and the numerous essential minerals and vitamins The absolute requirements for these substances cannot be stated since many have interrelated physiologic functions The amount of protein required in the diet depends upon the calories furnished by carbohydrate and fat The requirement for the B vitamin niacin is based upon the available amount of the amino acid tryptophan, and, similarly, the need for iron is related to the ascorbic acid content of the diet

However, we do know the relative amounts and ranges of many of the specific factors required for good health The caloric content must meet the basal metabolic need in order to maintain weight equilibrium, and it must provide for the activity of the individual The range for an adult may vary from 2000 to 5000 calories per day Generally, carbohy-

Table VIII.1. Desirable Ranges for Daily Intake of Certain Nutrients

	SEDENTARY	MODERATELY ACTIVE	VERY ACTIVE
Calories	1800–2000	2200–3200	3200–5000
Protein gm	50–100	50–100	50–100
Calcium gm	0 4–0 8	0 4–0 8	0 4–0 8
Iron mgm	12–15	12–15	12–15
Sodium gm	1–5	1–5	1 5
Vitamin A I U	3000–5000	3000–5000	3000–5000
Thiamine (vitamin B_1) mgm	1–2	1–2	1 2
Riboflavin (vitamin B_2) mgm	2–3	2–3	2–3
Niacin mgm	10–20	10–20	10–20
Ascorbic acid, mgm	40–75	40–75	40–75

drate provides 60 to 75 per cent of the required total, fat 10 to 40 per cent and protein 8 to 15 per cent Except for pregnant and lactating women the protein requirements of adults approximate 30 grams per day, but in practical nutrition twice this amount or more is desirable Therefore the recommended daily allowances of the more important food constituents are based on the theoretical minimal requirements with a substantial increment to provide for special needs and to afford a factor of safety (Table VIII 1)

Effect of Tropical Climate on Nutritional Requirements

The opinion is frequently expressed that tropical climates cause unusual changes in nutritional requirements Except in the matter of calories and water, there is little evidence to support this view The widely prevalent malnutrition there is largely an expression of insufficient supplies of protective foods, selectivity of diet determined by the cultural and religious backgrounds of the people and the direct and indirect effects of infection Many people in tropical climates are unable to obtain the basic foods essential for a good diet The problems are fundamentally agricultural and economic rather than climatic Other groups, because of religious beliefs or social practices, avoid available animal protein Still others prefer polished to unpolished rice Parasitic or other gastrointestinal infections may interfere with the absorption of specific food factors or utilize those available for their own economy at the expense of the host Systemic infections by their effect on the metabolism or the tissues of the host, may increase significantly the daily requirements for particular nutrients Thus the essential problem will vary from region to region depending upon the practices of man and only secondarily upon the effects of climate

Calories Energy requirement is decreased in the tropics since the higher environmental temperatures diminish the need for heat production The relative importance of temperature has, however, often been overemphasized Observers have been unduly impressed by the temporary anorexia which frequently follows sudden passage from the temperate to tropical climates An investigation of calorie requirements was conducted during World War II using United States and Canadian troops

stationed in various parts of the world All of the groups retained their usual food habits and all were engaged in the same types of duty Under these conditions a linear correlation was observed between voluntary calorie intake and climatic environment with the daily intake decreasing by 16 calories for each degree of increase in mean Fahrenheit temperature or 29 calories for each degree centigrade Since that study additional evidence relating the voluntary intake of troops to mean annual temperature has been obtained particularly in studies made by the Royal Air Force On the basis of these observations and of national averages of calorie intake in various climates the Second Caloric Requirement Committee of the United Nations Food and Agriculture Organization estimated that there is a 3 per cent decrease in caloric requirements for every 10° C of mean annual external temperature above the reference temperature of 10° C

Protein and Fat. Available evidence indicates that high environmental temperatures introduce no change of practical importance in human protein requirements Attention has been called to the low fat consumption in many tropical areas This appears to be due essentially to local economic conditions A low fat diet has been claimed repeatedly to be of value where conditions causing impaired liver function are widespread

Vitamins While it has been claimed that requirements for thiamine and for ascorbic acid are increased by heat the evidence in support of this assertion is unconvincing Similarly claims that tropical climates *per se* "predispose" to rickets are obscured by lack of control of other factors such as the availability of calcium and phosphorus Whenever regular exposure to sunshine is prevalent the appearance of rickets is prevented This probably explains the infrequent occurrence of rickets in the tropics in spite of low calcium and the possible "predisposing" effect of heat. The great preponderance of evidence indicates that vitamin requirements of healthy persons are essentially the same in temperate and in tropical climates

Water and Minerals. Water requirements are increased roughly in proportion to the amount of sweat secreted They may increase from 2 0 or 3 0 liters per day in a temperate climate to 13 liters or more during work in a hot environment Under extreme conditions the need for water may actually outstrip thirst Wartime studies demonstrated that the best level of performance is obtained when the water lost in sweat is replaced hour by hour While loss of minerals sodium chloride in particular is increased in individuals first exposed to hot climates acclimatization is accompanied by decreased salt concentration in sweat so that salt requirements are increased only slightly The trend in recent practice has been against providing salt to men working in the heat—either as tablets or as salinized drinking water—except possibly to unacclimatized individuals or in cases of unusual extremes of activity and temperature

Foods as Sources of Nutrients

Rice is the single most important food of many tropical regions because it is usually more plentiful but other predominantly carbohydrate foods such as corn and millet and root vegetables such as taro are widely used

Finally in the presence of a definite clinical syndrome functional changes occur in the small intestine which interfere with normal utilization of the diet and consequently operate still further to augment existing deficiencies Thus there is created a vicious progressive spiral in which both a primary dietary deficit and a secondary disturbance of normal physiology causing impaired absorption contribute to progression of the deficiency state

The operation of these varied factors upon population groups is well illustrated by studies of the nutritional status of the inhabitants of Madrid during the Spanish Civil War These observations can be used likewise to predict with a reasonable probability of accuracy the status of groups subjected to famine or near famine if the approximate duration of the period of deprivation is known During the siege of Madrid the available diet consisted mainly of starches Animal protein and good sources of the vitamin B complex were both seriously restricted The first noticeable effects of this deficient diet were indicative of a lack of adequate amounts of the B complex vitamins Thus functional neurologic disturbances appeared early Later a marked increase in the incidence of pellagra occurred particularly during the spring seasons of the second and third years Famine edema however did not appear until the third year of the war

During World War II internees in areas of the Far East developed beriberi because the limited food available to them was polished rice devoid of thiamine and other B vitamins Internees in Western Europe were fed on whole grain breads and potatoes reasonably good sources of the water soluble vitamins and few cases of the classic vitamin deficiencies developed In western Holland for example during the last six months of the war severe starvation was frequent but not vitamin deficiencies because with little food to metabolize the need for the B complex vitamins which function in various metabolic reactions is minimal

Although the most striking clinical phenomena occurring in the specific nutritional diseases may indicate a marked deficit of one particular substance or group of substances other important deficiencies exist as well Immediate institution of a completely adequate diet becomes therefore the essential procedure in the treatment of this whole group of conditions It is frequently necessary however to supplement dietary therapy by administration of pharmacologic preparations of certain of the vitamins and of ample amounts of particularly rich crude sources Additional amounts of certain minerals and an excess of biologically complete protein are likewise often required to obtain the most complete and most rapid response to treatment

Tropical Malnutrition

No striking deviation from temperate zone requirements except for water is thus characteristic of tropical conditions The tropical climate itself may play a secondary role in the evolution of certain nutritional diseases in that climatic factors such as wind exposure to sun and extreme heat may influence nutritional dermatoses The effect of sunlight

on skin appearance in pellagra is well known Local climatic conditions may contribute to the differences in skin abnormalities associated with kwashiorkor in various regions of the world But the essential significance of tropical nutritional diseases lies in fields other than human physiology An obvious and well known factor is the prevalence of parasitic and infectious diseases These will often contribute to decreased intestinal absorption sometimes to increased requirements and usually to some degree of anorexia Another and more important factor is the agricultural economic and social status of many tropical populations Many such peoples subsist on a diet based almost exclusively on one principal starchy staple food—rice millet or corn for example The classic deficiency diseases characteristic of such diets could perhaps best be termed "diseases of society" rather than "tropical diseases" despite their geographic localization

Pathologic conditions associated with malnutrition and found in the tropics may be classed in four categories

1 Syndromes which are essentially of dietary origin even though they may be complicated by parasitic and infectious conditions for example beriberi pellagra and kwashiorkor

2 Conditions which are probably of nutritional origin such as tropical ulcer sprue pernicious anemia and certain urolithiases

3 Conditions of unknown etiology in which nutritional factors appear to be important such as primary carcinoma of the liver and certain pancreatic fibroses

4 Diseases the primary causes of which are non nutritional but in which nutritional factors affect directly the response to the pathogenic agent or which contribute indirectly to the development of complicating malnutrition

Important examples of the first two categories only will be considered in this section The recognized clinical syndromes present one part of the picture of malnutrition Nutritional diseases characteristically develop as multiple deficiencies The signs and symptoms characteristic of several nutritional syndromes commonly appear simultaneously or in succession

54

Pellagra

Synonyms Mal de la rosa mal del sole psilosis pigmentosa Alpine scurvy chichism (northern South America)

Definition Pellagra is the principal manifestation of a severe deficiency of niacin generally complicated by deficiencies of other B vita

mins It is characterized clinically by a red, sore tongue, disturbances of the alimentary tract, symmetrical dermatitis and changes in the central and peripheral nervous systems

Distribution. The disease has a world wide distribution It is generally associated with the consumption of diets containing an excessive proportion of corn (maize) The disease is more prevalent during the

to prolonged ingestion of a low nicotinic acid The amino acid trytophan can be converted to niacin by the human organism, so that low levels of both of these nutrients must generally be present for pellagra to appear Diets high in corn and containing little or no meat, milk, fish or other good sources of protein are pellagragenic The importance of the amino acid composition of the diet is illustrated by the fact that wheat diets are not pellagragenic in spite of a niacin content often lower than that of corn diets

Lack of niacin interferes with the formation and the function of two essential respiratory enzymes, the diphosphopyridine and triphosphopyridine nucleotides *The effects of this deficiency can therefore be expected to be widespread Less severe deficiencies of niacin produce milder* symptoms

While ... essential etiologic ... which interfere ... ra preventing food factors contribute to the prevalence of pellagra Among these, amebic dysentery, hookworm infection, malaria and cirrhosis of the liver are of particular importance in tropical regions Secondary pellagra is one of the secondary deficiency diseases sometimes associated with chronic alcoholism

As in other deficiency diseases, the phenomena characteristic of pellagra are usually accompanied by a relative lack of other essential nutrients *Cheilosis responding to riboflavin administration* and peripheral neuritis responding to thiamine treatment are frequently seen as complications

Pathology. No characteristic or constant *pathologic changes are* observed In acute cases there is active inflammation of certain skin areas and of the mucosa, particu... Repeated attacks lead to atrophy and ... egions

Clinical Characteristics ... le and the disease may be acute, subacute or chronic The onset is usually gradual with asthenia, loss of weight, mental depression and a sore red tongue

Dermatitis may also occur Characteristically it is symmetrically distributed, *affecting areas which are exposed to irritation,* such as the dorsum of the hands and wrists, the elbows, face, neck the skin beneath the breasts, the perineal region, the patellar areas and the dorsum of the feet In most instances it is restricted *to parts exposed to the sun In the early* stage there is erythema resembling sunburn This may be followed by vesiculation and bulla formation The skin becomes thickened and roughened, and, as the acute inflammation subsides, brownish pigmentation

remains Repeated attacks lead to marked atrophy of the skin (Figs VIII 1 VIII.2)

Lesions of the tongue and mouth are usual Acute glossitis and stomatitis may progress to extensive ulceration Simultaneously there is fissuring at the angles of the mouth The tongue is swollen denuded of its papillae and often painful and extremely sensitive (Fig VIII 3)

Hypochlorhydria or achlorhydria are common and there may be diarrhea or alternating periods of diarrhea and constipation The stools are not abnormal in color and contain no excess fat

Pellagra is accompanied by a variety of symptoms referable to the nervous system In the early stages the picture is that of neurasthenia which increases in severity with progression of the disease In advanced and long standing cases true psychoses occur In these cases peripheral neuritis spastic gait and other indications of organic involvement are not uncommon

Diagnosis The four cardinal symptoms—dermatitis glossitis gastrointestinal symptoms and psychic disturbances—are characteristic of the well developed acute case

Diagnostic difficulties may be encountered in the early stages of the disease or in advanced chronic cases in which the characteristic acute phenomena are lacking The combination of pigmentation and atrophy of exposed skin areas smooth atrophy of the tongue and the picture of



Figure VIII.1

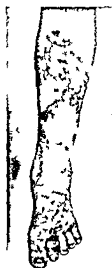


Figure VIII 2

Figure VIII 1 Acute pellagra—dermatitis of hand and wrist (Courtesy of Dr Julian Ruffin, Duke Hospital.)

Figure VIII.2. Acute pellagra—dermatitis of exposed areas of leg and foot (Courtesy of Dr Julian Ruffin Duke Hospital)



Figure VIII 3 Acute pellagra—characteristic dermatitis of exposed skin of face and neck, acute glossitis (Courtesy of Dr Julian Ruffin Duke Hospital)

neurasthenia should arouse suspicion Analysis of urine for N[1] methyl nicotinamide content may be of help Normal excretion is usually over 3 mgm per day Levels of excretion below 1 mgm reinforce the presumption of pellagra or prepellagrous state

Treatment 1 High protein high vitamin diet

2 Nicotinic acid or nicotinic amide 300 to 500 mgm daily in divided doses

3 Therapeutic doses of the B complex vitamins in particular thiamine chloride 5 to 10 mgm daily as indicated

Prophylaxis The prophylaxis of pellagra is based upon an adequate diet

55

Beriberi

Synonyms Polyneuritis endemica barbiers kakke (China and Japan) maladie des sucreries (French Antilles) hinchazon (Cuba) inchacao or perneiras (Brazil) maladie des jambes (Louisiana) alcoholic neuritis

Definition Beriberi is a nutritional disease due to deficiency of vitamin B_1 (thiamine) and other vitamins It exhibits acute and chronic forms characterized by peripheral neuritis and in severe cases by con gestive heart failure It may occur in all age groups

Distribution Beriberi has been widespread in the past in the Orient and in areas of the tropics where polished rice is an important dietary staple It has also been prevalent in Labrador Newfoundland and Ice land where the winter diet is restricted largely to white flour and other non vitamin bearing foods

Etiology Primary beriberi is the result of prolonged subsistence on a deficient diet Secondary beriberi may occur as a complication of other disease states attended by deficient absorption incomplete utilization or unusual requirements for thiamine such as occur with elevated levels of metabolism

Epidemiology The incidence of beriberi varies with dietary habits and with the availability of foods providing adequate amounts of es sential food factors It is seen most commonly in men and there is evi dence to indicate that hard physical labor is a precipitating factor Among women the disease occurs particularly during pregnancy and lactation Infantile beriberi is a frequent cause of death among breast fed infants in the endemic areas Although it is not an infectious disease "epidemics" have been noted when outbreaks of diarrheal disease have occurred in populations subsisting on borderline diets since diarrhea in creases the physiologic requirements of the individual and diminishes the utilization of specific food factors

Pathology The heart and the nervous system are involved pri marily The cardiac changes are predominantly hypertrophy and subse quent dilatation The weight of the heart is frequently considerably increased No specific lesions have been identified and the observed path ologic changes are often insufficient to account for the deaths from cardiac failure The effects on tissues other than those of the nervous system are those of congestive heart failure

Degenerative lesions without evidence of inflammation may be found throughout the nervous system They occur in the peripheral nerves the spinal cord spinal ganglia the nuclei of the medulla and pons and in the structures of the autonomic nervous system In the spinal cord the changes predominate in the posterior columns and in both the anterior and posterior nerve roots There is destruction of myelin sheaths which may be accompanied by fragmentation of the nerve fibers and atrophy of the nerve cells Usually these changes affect only part of the fibers con stituting a nerve trunk The extent of these changes depends upon the duration and the severity of the disease Of the peripheral nerves the sciatic is most frequently involved and evidence of this appears early Of the cranial nerves the vagi and the phrenics are most frequently af fected With the disturbance of nervous innervation there is secondary atrophy of the muscles

Clinical Characteristics Four clinical types of the disease are recognized dry beriberi wet beriberi infantile beriberi and atypical beriberi

There are no specific phenomena which are necessarily common to all types The clinical manifestations of the disease fall into three general categories those referable to degenerative lesions of the nervous system those resulting from cardiac hypertrophy and dilatation and the secondary effects of edema and anasarca The onset may be rapid or gradual the condition may become chronic and recurrences of the acute form are frequent The disease is commonly ushered in by the development of muscle weakness anorexia and neurasthenia Tachycardia and cardiac enlargement usually become evident early There is often slight anemia As the disease becomes established progressive peripheral nerve palsies appear

Dry Beriberi The onset is usually gradual and the outstanding symptom is progressive weakness of the muscle groups which are most used This most commonly appears in the extensor muscles of the thighs and a significant early symptom in many instances is inability to rise from a squatting position With the weakness there is atrophy of the muscles Sensory disturbances appear at the same time but are usually less prominent These may take the form of paresthesias hyperesthesias or hypesthesias In severe cases many muscle groups may be affected and the clinical picture is that of flaccid paralysis muscular atrophy with or without evidence of cardiac enlargement and tachycardia

Wet Beriberi In wet beriberi the clinical picture is predominantly that of acute congestive failure with relatively little evidence of nervous system involvement Signs of neuropathy however can be elicited in most instances The onset is frequently rapid and acute and the marked edema may mask the presence of significant muscle atrophy

Electrocardiographic changes are common and characteristically consist of alterations in the T waves and prolongation of the electrical systole (Q–T) Sudden collapse is not infrequent The exact mechanism of this form of the disease is uncertain but it seems probable that both the heart and the peripheral vascular system are concerned

Infantile Beriberi Breast fed infants of mothers subsisting on a diet deficient in thiamine develop an acute condition differing markedly from the disease of adults In the usual type the onset is preceded by a period of diminished urine secretion accompanied by progressively increasing edema If treatment is withheld acute cardiac failure suddenly supervenes and death may follow rapidly With the appearance of the acute phenomena the child cries constantly and meningismus and convulsions may occur

In the more uncommon dry type of infantile beriberi edema and circulatory disturbances are not prominent There may be vomiting constipation anorexia loss of weight pallor fretfulness and a characteristic plaintive cry of aphonia The muscles are hypersensitive but there is usually little definite evidence of nervous system disease

Atypical Beriberi The clinical picture of the disease may be modified by other nutritional disorders such as scurvy pellagra or nutritional edema So called ship beriberi and land scurvy fall in this category as does the polyneuritis of alcoholic beriberi

Diagnosis The essential diagnostic features are signs and symptoms of peripheral neuritis with weakness of the most used muscle groups Hyperesthesia of muscles particularly the plantar muscles and the gastrocnemius is common and significant An important and early physical sign is reduction or loss of vibratory sensation over the affected distal portions of the extremities with diminution or loss of distal proprioceptive sense Tendon reflexes are later diminished and then lost In severe cases marked muscle atrophy occurs Measurement of thiamine excretion in the urine may provide confirmatory evidence The range considered to be normally 100 to 200 μg daily is markedly reduced in clinical cases of beriberi

The occurrence of diminished urinary secretion with edema in a breast fed infant should immediately arouse suspicion and lead to prompt institution of specific therapy

Beriberi must be differentiated from other types of peripheral neuritis tabes dorsalis postdiphtheritic paralysis and acute heart failure due to other causes

The following eight criteria have been suggested to differentiate cardiac disease due to other causes from that of beriberi

1 Enlarged heart with normal sino atrial rhythm
2 Dependent edema
3 Elevated venous pressure
4 Peripheral neuritis
5 Nonspecific changes in the electrocardiogram
6 Lack of other recognized cause of heart failure
7 Grossly deficient diet for at least three months
8 Clinical improvement with reduction of heart size after specific treatment

Treatment 1 Thiamine chloride 5 to 10 mgm parenterally twice daily

The wet form of beriberi must be treated by absolute rest and heavy dosage of thiamine which should be administered both intravenously and subcutaneously The appropriate measures for the management of acute congestive failure should be used as they may be indicated

Infantile beriberi should be treated by appropriate alteration of the mothers diet and the infant should receive heavy doses of thiamine parenterally

Prognosis Deaths from the acute form of wet beriberi are not infrequent The chronic form may leave permanent disability such as muscle weakness or flaccid paralysis due to nerve cell degeneration Recovery from the disease in adults is slow The muscle weakness and neuritis frequently persist for months Infantile beriberi on the other hand responds very rapidly and completely when treatment is adequate

56

Sprue

Synonyms Psilosis Ceylon sore mouth Cochin China diarrhea

Definition Sprue is a chronic afebrile relapsing disease characterized by sore tongue flatulence steatorrhea progressive emaciation cachexia and anemia The latter is at first hypochromic, becoming hyperchromic and in the terminal stages of untreated cases occasionally aplastic

Distribution It occurs predominantly in the Far East in India and Ceylon and in the Western Hemisphere in Puerto Rico It occurs sporadically in the United States and other parts of the world with the exception of Africa where it is extremely rare

Etiology The exact etiology is unknown The fully developed syndrome is the expression of mixed multiple nutritional deficiencies among which folic acid deficiency appears to play the dominant role The fact that daily administration of pteroylglutamic (folic) acid relieves the symptoms of sprue might be interpreted to indicate that sprue is a specific deficiency disease The etiology is confused however and some of the epidemiologic data have suggested that the primary mechanism may be of infectious origin Despite this nutritional considerations dominate both the etiologic and the therapeutic aspects of the disease

Digestion of protein carbohydrate and fat is normal but there is incomplete absorption of fatty acids and glucose This dysfunction is associated with flatulence and bulky gaseous acid stools which contain large amounts of unabsorbed fatty acid crystals There is likewise excessive loss of calcium in the form of insoluble calcium soaps in the feces Hypochlorhydria is the rule and achlorhydria occurs occasionally

It has been suggested that the basic defect—loss of ability to absorb fatty acids glycerol and glucose—is due to failure of phosphorylation and to loss of phosphorus as the result of failure of phospholipid formation

Epidemiology It has not been possible adequately to explain the geographic distribution of the disease Its incidence is not associated with any particular type of diet or dietary deficiency It is a disease characte[illegible] the upper[illegible]

P[illegible] process

The findings at postmortem are limited essentially to wasting and atrophy of the various organs and of the body as a whole

In the advanced stage showing macrocytic anemia the bone marrow is

characteristically hyperplastic as in pernicious anemia In still later cases the marrow may be aplastic and contain little active hematopoietic tissue

Clinical Characteristics The clinical picture varies greatly and the onset is gradual and insidious In the majority of cases however the three cardinal symptoms—sore tongue and mouth flatulent indigestion and diarrhea—are present when the disease is fully established These features appear simultaneously or in succession in any order

Mouth lesions are prominent in most instances and usually precede

and the esophagus may cause severe dysphagia Salivation may be troublesome

Flatulence at first mild and intermittent and frequently relieved by evacuation of a stool gradually becomes continuous and increasingly severe Eventually extreme and persistent abdominal distention may be a source of much distress to the patient

In the early stages the diarrhea is usually intermittent and frequently mild coming in the early morning accompanied by a sense of urgency Gradually the stools become increasingly voluminous gassy foul and light yellow or gray At first there may be only one evacuation each day later the number increases and the stools become more fluid and irritating

Spontaneous remissions of symptoms are characteristically followed by increasingly severe relapses The latter result in progressive papillary atrophy of the tongue weight loss and increasing asthenia In the early stages of the disease there is commonly a moderate microcytic anemia

In advanced cases emaciation is often extreme The tongue is characteristically smooth fiery red painful and extremely sensitive to heat and condiments There is marked mental depression and severe anorexia Paresthesias of the extremities may be present The patient often complains of epigastric distress and flatulence The skin especially of the face and the flanks frequently exhibits muddy pigmentation The abdomen is markedly distended and individual coils of intestines are visible In some instances there may be evidence of subacute combined degeneration of the cord Stools are frequent liquid white or yellowish white in color abnormally bulky and gassy Evacuation may be painful owing to excoriation of the anus At times severe tetany may occur and in some instances there may be bleeding due to lack of vitamin K

In the advanced case the anemia is macrocytic and may be severe Gastric analysis will reveal hypoacidity or anacidity but not achylia

the phosphorus content is normal or somewhat low Hypoproteinemia is comm estion of 1 5 gr at blood sugar per 100 ml Intravenous administration of 0 2 gram of glucose per kilogram of

body weight however gives a normal blood sugar curve Vitamin A tolerance tests reveal a flat curve indicative of poor fat absorption

Roentgen examination of the small intestine reveals characteristic functional disturbances The barium tends to accumulate in dilated coils The mucosal pattern is much coarser than normal and the progress of the opaque meal is slow and intermittent Barium enema may reveal a markedly dilated and atonic colon

Diagnosis The characteristic case with glossitis hyperchromic anemia and steatorrhea presents little diagnostic difficulty The typical clinical phenomena however may not all be present a feature which has led to the clinical classification of "complete and "incomplete" sprue The differential diagnosis entails differentiation from chronic pancreatitis carcinoma of the pancreas pernicious anemia gastrojejunocolic fistula and regional enteritis The following features are characteristic of sprue

1 Steatorrhea with normal splitting of fat and normal digestion of starch and protein

2 Flat glucose tolerance curve on oral administration

3 Normal glucose tolerance curve on intravenous administration

4 In severe cases macrocytic anemia with megaloblastic arrest of the bone marrow

Treatment 1 High protein high vitamin low fat diet In cases with marked flatulence it may be necessary to restrict starches and sugars

2 Daily intramuscular injection of 15 mgm of folic acid followed by maintenance dosage of 5 mgm by mouth when the patients condition permits

3 Parenteral administration of vitamin K or oral administration of a water soluble vitamin K preparation

4 If folic acid is not available brewers yeast 60 grams or tiki tiki extract of rice polishings 30 grams should be given daily by mouth and concentrated aqueous liver extract 5 ml intramuscularly each day

When treatment is effective it is followed by rapid healing of the mouth lesions and progressive improvement in the intestinal features Stools become less frequent the volume is diminished the consistency improved the color returns toward normal and the amount of unabsorbed fatty acids decreases Lack of gastrointestinal and of hematologic response to folic acid should lead to doubt of the diagnosis The response to vitamin B_{12} should then be tested

Prognosis The prognosis depends to a large extent upon the duration and severity of the disease prior to the institution of adequate therapy Mild cases may ultimately be able to resume a normal diet without medication More commonly fats in the diet must be restricted permanently and parenteral injections of liver continued at intervals of

57

Kwashiorkor

Synonyms Malignant malnutrition (South Africa) fatty liver disease of children (West Indies) fatty liver of Brahmin children (India) bouffissure d'Annam (Vietnam) sindrome pluricarencial infantil (Central America) The syndrome merges into other nutritional syndromes such as marasmus and Mehlnahrschaden

Definition Kwashiorkor is a nutritional syndrome in which a deficiency of good quality protein appears to be a dominant factor It is found among many poor populations especially among young children and characteristically the following occur (1) retarded growth and maturation (2) apathy sometimes irritability (3) anorexia (4) diarrhea sometimes vomiting (5) alteration in color and texture of the hair and sometimes of the nails (6) lesions of the skin marking varying degrees of hyperkeratosis dyspigmentation and desquamation (7) edema (8) marked fatty infiltration of the liver (9) a heavy mortality in the absence of proper dietary treatment

Distribution The various synonyms for the disease testify to its widespread character It is found wherever tropical peoples subsist on [illegible]

India Its prevalence within populations can be extremely high It has been claimed that practically every child in certain African and Central American regions for example has or has had some degree of protein malnutrition bordering on kwashiorkor

Etiology Lack of proteins particularly complete proteins seems to be principally responsible for the characteristic pathologic changes These appear to be the result of a deficiency of good quality protein in general rather than a deficiency of a single amino acid The disease is not observed during the period of breast feeding as long as the supply of maternal milk is adequate It closely follows weaning and transfer of the child to starch gruels when maternal milk is replaced by low grade and dilute foodstuffs

In addition to this universal deficiency, it appears that additional inadequacies of the various local diets determine the preponderance of various symptoms

Pathology and Clinical Characteristics The following signs symptoms and pathologic findings are observed (Fig VIII 4)

body weight, however, gives a normal blood sugar curve Vitamin A tol erance tests *reveal a flat curve indicative of poor fat absorption*

Roentgen examination of the small intestine reveals characteristic functional disturbances The barium tends to accumulate in dilated coils *The mucosal pattern is much coarser than normal* and the progress of the opaque meal is slow and intermittent Barium enema may reveal a markedly dilated and atonic colon

Diagnosis. The characteristic case with glossitis, hyperchromic anemia and steatorrhea presents little diagnostic difficulty The typical clinical phenomena, however, may not all be present, a feature which has led to the clinical classification of "complete" and "incomplete" sprue The differential diagnosis entails differentiation from chronic pancreatitis carcinoma of the pancreas, pernicious anemia, gastrojejunocolic fistula and regional enteritis The following features are characteristic of sprue

1 Steatorrhea with normal splitting of fat and normal digestion of starch and protein

2 Flat glucose tolerance curve on oral administration

3 Normal glucose tolerance curve on intravenous administration

4 In severe cases, macrocytic anemia with megaloblastic arrest of the bone marrow

Treatment. 1 High protein, high vitamin, low fat diet In cases with marked flatulence it may be necessary to restrict starches and sugars

2 Daily intramuscular injection of 15 mgm of folic acid followed by maintenance dosage of 5 mgm by mouth when the patient's con dition permits

3 Parenteral administration of vitamin K, or oral administration of a water soluble vitamin K preparation

4 If folic acid is not available, brewer's yeast 60 grams, or tiki tiki extract of rice polishings, 30 grams, should be given daily by mouth, and concentrated aqueous liver extract 5 ml intramuscularly each day

When treatment is effective, it is followed by rapid healing of the mouth lesions and progressive improvement in the intestinal features Stools become less frequent, the volume is diminished, the consistency improved, the color returns toward normal, and the amount of unab [illegible] and of hematologic [illegible] The response

Prognosis. The prognosis depends to a large extent upon the dura tion and severity of the disease prior to the institution of adequate therapy Mild cases may ultimately be able to resume a normal diet without medication More commonly fats in the diet must be restricted permanently and parenteral injections of liver continued at intervals of one to two weeks The character of the stools, the amount of unabsorbed fatty acids in the feces and the presence or absence of flatulence provide satisfactory guides to therapy

57

Kwashiorkor

Synonyms Malignant malnutrition (South Africa) fatty liver disease of children (West Indies), fatty liver of Brahmin children (India) bouffissure d Annam (Vietnam) sindrome pluricarencial infantil (Central America) The syndrome merges into other nutritional syndromes such as marasmus and Mehlnahrschaden

Definition Kwashiorkor is a nutritional syndrome in which a deficiency of good quality protein appears to be a dominant factor It is found among many poor populations especially among young children and characteristically the following occur (1) retarded growth and maturation (2) apathy sometimes irritability (3) anorexia (4) diarrhea sometimes vomiting (5) alteration in color and texture of the hair and sometimes of the nails (6) lesions of the skin marking varying degrees of hyperkeratosis dyspigmentation and desquamation (7) edema (8) marked fatty infiltration of the liver (9) a heavy mortality in the absence of proper dietary treatment

Distribution The various synonyms for the disease testify to its widespread character It is found wherever tropical peoples subsist on

India Its prevalence within populations can be extremely high It has been claimed that practically every child in certain African and Central American regions for example has or has had some degree of protein malnutrition bordering on kwashiorkor

Etiology Lack of proteins particularly complete proteins seems to be principally responsible for the characteristic pathologic changes These appear to be the result of a deficiency of good quality protein in general rather than a deficiency of a single amino acid The disease is not observed during the period of breast feeding as long as the supply of maternal milk is adequate It closely follows weaning and transfer of the child to starch gruels when maternal milk is replaced by low grade and dilute foodstuffs

In addition to this universal deficiency it appears that additional inadequacies of the various local diets determine the preponderance of various symptoms

Pathology and Clinical Characteristics The following signs symptoms and pathologic findings are observed (Fig VIII 4)



Figure VIII 4 Kwashiorkor in young native of the Belgian Congo Note the white hair skin discoloration and general edema (Courtesy Dr Louis Van den Berghe photo IRSAC Belgian Congo by Macot)

Retardation of Growth This begins at the late breast feeding, weaning and postweaning ages It is fundamental to kwashiorkor but is also common to other conditions such as undernutrition due to lack of available calories or to anorexia marasmus and atrophy

In spite of the serious growth retardation the infant with kwashiorkor does not always look emaciated or starved If he has been provided with considerable starch or sugar while he was deprived of protein his sub cutaneous fat may be appreciable and particularly if mild edema is present and dermatosis absent the infant may give a superficial appear ance of good nutrition

Edema Serum albumin is generally reduced in kwashiorkor and is almost universally reduced to a marked degree in edematous kwashi orkor Relative hyperglobulinemia is often present whether as a com pensatory reaction as a result of parasitic infection or secondary to liver damage

Liver The liver is usually not palpable but is universally found to be extremely infiltrated with fat frequently to such an extent that the normal lobulation is hardly recognizable

Depigmentation and Dermatoses There may be both a reduction of quantity of hair and skin pigment and qualitative alteration This must be distinguished from hypopigmentation due to admixture with people of lighter color or inborn mutations ("half albinos") Skin dyspigmenta tion due to kwashiorkor can be patchy or diffuse and in some cases may cover the entire body Hyperpigmentation is also frequently observed

Dermatoses do not appear to be the same in various regions of the

world and therefore probably have several different origins A most common form is an eruption of sharply defined black varnished patches on areas exposed to irritation (diaper area buttocks, back) and not confined to areas exposed to sunlight (hands and face), thus permitting differentiation from pellagra The hyperpigmented areas may become
may blister

seen in ex-
treme cases in many areas of the world

Gastrointestinal Disorders, Pancreas and Duodenal Enzymes Mucosal lesions and atrophy, diarrhea and deficient intake may be all part of a vicious circle Pancreatic fibrosis is observed but is by no means a constant finding Drastically reduced lipase, trypsin and amylase may be a result of the atrophy of the pancreas and duodenal mucosa

Psychic Changes Children with kwashiorkor are usually apathetic and anorexic They appear extremely miserable and may be irritable, although they rarely cry

Mortality in Untreated Cases The mortality in the untreated syndrome is very high Recent studies suggest that the heavy mortality is associated with irreversible biochemical changes In the absence of proper treatment the mortality is seldom less than 30 per cent, and in some areas goes up to 100 per cent

Treatment. Well planned treatment is based on our understanding of the primary factor in the etiology—primary deficiency of good quality proteins, often associated with vitamin deficiency The degree of severity of the case, the nature and extent of dehydration and electrolyte imbalance, and the presence and extent of intestinal parasitosis and other infections are also important considerations

The main treatment is dietary In children over three years old whose

days) Some fat can be included as a source of calories after the first few days of treatment In younger children whose digestive troubles are slight, diluted milk (*two parts of fresh milk to one part of water or rice water*) may be given In more severe cases increasing amounts of skim milk should be administered Skim milk is sometimes acidified as well as diluted to facilitate digestion Within two weeks, the caloric intake should be built up to 100 to 120 calories per kilogram of body weight

Clinical experience has shown that the administration of the vitamin B complex *in large doses is not only useless* but *sometimes makes the* condition worse Vitamins C and A in physiologic doses (the water emulsified form of synthetic vitamin A is preferable) are often given in the early treatment, as these are the two vitamins lacking in the diet based on skim milk Results of use of lipotropic agents have been poor Vitamin B_{12} and folic acid have been used when anemia is present and the diet deficient in these nutrients Ferrous sulfate (300 to 600 mgm

orally per day) may be introduced in the course of the first or second week of treatment Penicillin may be given from the outset as a routine precaution against possible infection which in children with kwashiorkor may not manifest itself by fever or by elevated white cell count Children do better if they receive personal attention and affection throughout treatment

The following emergency treatments have given good results in severe cases (1) in marked dehydration following diarrhea and vomiting (with or without edema) appropriate intravenous electrolyte solutions (2) in the presence of shock or extreme anemia blood transfusions (3) the treatment of specific diseases such as malaria is started from the outset by using the less toxic drugs The treatment of intestinal parasitosis is not undertaken until the child has recovered sufficiently to start treatment without danger

Prognosis in Treated Cases The short term prognosis of mild cases given full treatment is good The frequency of multiple episodes is high when home conditions are unfavorable Recurrences take place not only in children taken home by parents before the cure is complete but also less usually in children who leave the hospital "clinically cured" Relapse usually occurs three to six months after the child has left the hospital The clinical state during relapse is usually similar and often more serious than at first admission The mortality rate in such cases continues high

The prognosis of successfully treated cases over a longer or life span period is not known It is unlikely, from their world distribution that cirrhosis and primary carcinoma of the liver on the one hand and kwashiorkor on the other are related in any direct cause and effect manner Adult cirrhosis may well result from the effects of continued protein deficiency and parasitosis infection and toxic factors on a liver already damaged in childhood by kwashiorkor A similar situation may exist with respect to primary carcinoma of the liver

Prophylaxis Proper prevention is based on

1 Increasing the supply of proteins both animal and vegetable This entails development of milk producing livestock—cattle sheep and goats —and the expansion of fisheries and fish farming Proper mixtures of vegetable protein must also be developed in particular by increasing availability of pulses nuts and green vegetables

2 Eliminating the hungry months" during which incidence of kwashiorkor increases by developing cash crops and other additional sources of income

3 "Supplementary feeding" programs directed at infants and young children with emphasis on foods providing adequate amounts of good quality protein

4 Education With the best intentions young mothers in poor tropical countries commit many grave faults in the nutrition of their children However when proper nutrition education programs are in effect it is usually found that changes in traditional patterns of infant and small child feeding can be introduced fairly rapidly Maternity and child health centers have had considerable influence on nutrition habits Family

dietary habits can also be influenced through schools, although in underdeveloped areas many girls do not attend school

5 Social welfare In poor areas there are usually substantial numbers of small children who suffer from simple neglect This situation can be remedied through the work of strong social agencies, which in turn must be educated in the nutritional requirements of this age group

58

Nutritional Edema

Synonyms. War edema, famine edema, prison edema

Definition. This condition is a nutritional disorder following long continued subsistence on a diet deficient in biologically complete protein It is characterized by changes in the concentration of the plasma proteins altered osmotic tension of the blood edema and anasarca

Incidence. This disease occurs particularly in famine areas It was widely prevalent in Central Europe during and immediately after the first World War and has occurred in India, Mauritius, Fiji and Java, and in Spain during the Spanish Civil War It occurs endemically as a complication of other nutritional diseases

Etiology. Nutritional edema develops when the diet is limited in total calories and the average protein content is less than 50 grams per day The appearance of the clinical syndrome is preceded by a prolonged period of negative nitrogen balance In the early stages the total plasma protein is unchanged, the albumin somewhat reduced and the globulin correspondingly increased Later the total protein is reduced and there is inversion of the normal albumin globulin ratio accompanied by disturbances of osmotic relationships and by water retention within the tissues

The normal values for the plasma proteins are

Total protein	6 5 to 8 5 gm per 100 ml
Albumin	4 2 to 5 7 gm per 100 ml
Globulin	1 3 to 3 0 gm per 100 ml

Clinical Characteristics. The development of the characteristic clinical picture is usually preceded by progressive weight loss due to the limited caloric intake As the chemical imbalance is established, further weight loss is checked by water retention and may be followed by an actual weight gain

In the early stages there is marked pitting edema of the lower ex

tremities later this becomes generalized and if progressive leads to general anasarca

Diagnosis The occurrence of edema in individuals subjected to famine conditions is suggestive The diagnosis is based upon fluid retention in the absence of congestive heart failure or significant renal disease and is confirmed by determination of the plasma proteins and demonstration of inversion of the albumin globulin ratio

Treatment The treatment of nutritional edema is essentially the institution of a high protein high vitamin diet which should be arranged to provide 120 to 150 grams of animal protein per day and to restrict salt and fluids

Epidemic Dropsy

Epidemic dropsy is believed to be nutritional edema complicating other nutritional disorders such as pellagra and beriberi It has appeared in mass outbreaks especially in India and is often accompanied by the neurologic symptoms and signs of beriberi and by erythematous skin lesions followed by pigmentation of exposed areas that is suggestive of endemic pellagra

59

Osteomalacia

Synonym Adult rickets

Definition Osteomalacia is a calcium phosphorus deficiency disease characterized by a negative balance of calcium and phosphorus and by deficient calcification of all osteoid tissue It is a disease primarily of women particularly during pregnancy and lactation and increases in severity with each successive pregnancy

Distribution It is widely endemic in north India China and Japan and occurs sporadically in Central Europe

Etiology Osteomalacia and rickets are the same disease Continuous resorption and new bone formation occur and there is failure of calcification of newly formed osteoid tissue because of insufficient absorption of calcium and phosphorus from the diet

Failure of calcium phosphorus absorption may be due to deficien diet abnormal dietary calcium phosphorus ratio steatorrhea or vitamin D deficiency Usually several of these factors are operative particularly lack of calcium and phosphorus in the diet and insufficient vitamin D The elevated mineral demands of pregnancy and lactation upon the maternal organism are important factors in the progression of the disease

Pathology The abnormal ossification produces gross progressive skeletal deformities especially of the pelvis thorax spine and long bones The bones become soft and flexible and the deformities are more frequently the result of bending than of fracture The bone cortex is thin the trabeculae are greatly reduced in number or may be absent

Microscopic examination reveals deficient calcification Osteoclasts are present in normal numbers while osteoblasts are very numerous

Clinical Characteristics The symptom picture is dominated by weakness bone pains and often generalized aching Bony tenderness is common and severe tetany may occur Symptoms are particularly acute during pregnancy and lactation The process characteristically remains relatively stationary in intervals between pregnancies

Progression of the disease leads to great deformity and disability Distortion of the bony pelvis causes difficult labor or makes parturition impossible

Diagnosis The marked deformities particularly of the lower extremities the thorax and the spine are suggestive in endemic areas X ray examination of the skeleton reveals generalized osteoporosis and the vertebrae often show biconcave deformity the so called "fish vertebrae" The diagnosis is established by blood chemistry findings In severe cases the serum calcium and phosphorus are low and the serum alkaline phosphatase increased In mild cases the calcium may be normal or only slightly reduced whereas the phosphorus is below normal levels and the phosphatase slightly increased

Differential diagnosis entails differentiation from other osteoporotic diseases particular difficulty is encountered with the osteoporotic form of hyperparathyroidism The blood chemistry findings in the latter condition are distinctive however The serum calcium is elevated the phosphorus low and the phosphatase is above normal levels

Treatment Treatment of the disease can protect only against further deformities It consists of the institution of a diet high in calcium and phosphorus and the administration of 10 000 to 50 000 units of vitamin D daily

60

Vitamin A Deficiency and Tropical Macrocytic Anemia

Vitamin A Deficiency

Distribution Vitamin A deficiency is widely prevalent in the tropics especially in those regions where other nutritional deficiency conditions are common

Etiology It usually occurs as a primary response to a diet which provides an insufficient supply of the vitamin or less frequently it may be a secondary complication of diseases which are associated with defective absorption of fats

Clinical Characteristics Vitamin A deficiency is characterized by skin changes reduced adaptability to darkness eye lesions and lesions of the nervous system In many regions of Africa and India a majority of children present skin changes which respond to vitamin A administration and many hospitalized patients show evidence of xerophthalmia The characteristic signs of vitamin A deficiency are as follows

Skin Changes Synonyms toad skin phrynoderma shark skin keratosis pilaris lichen pilaris lichen spinulosis Darier's disease

The usual changes in the skin include dryness and roughness followed by eruption of hyperkeratotic papillae Some hyperkeratotic changes associated with vitamin A deficiency do not respond to vitamin A treatment and presumably have a different origin in spite of their similarity The hair becomes dry and brittle and the nails develop transverse or longitudinal ridges

Eye Changes Adaptability to darkness is impaired producing so called "night blindness There may be photophobia xerosis and Bitot's spots In extreme cases keratomalacia may lead to corneal ulceration panophthalmitis and loss of the eyes

Nervous System Changes The susceptibility of the nervous system to vetches (*Lathyrus* sp) is increased by vitamin A deficiency The clinical syndrome lathyrism is common in parts of India and has been reported from other regions of the world It is characterized by a spastic paraplegia

Treatment Effective treatment of the conditions due to lack of

vitamin A requires daily administration of large doses from 50 000 to 100 000 International Units

Tropical Macrocytic Anemia

Tropical macrocytic anemia appears to be a response of the hema topoietic system to a nutritional deficiency Although it may resemble certain aspects of sprue there is no interference with intestinal absorp tion Like sprue it responds satisfactorily to treatment with folic acid

IX

Miscellaneous Conditions

61

Epidemic Hemorrhagic Fever

Robert L Hullinghorst

Synonyms. Songo fever, Far East hemorrhagic fever, endemic hemorrhagic nephroso nephritis Kokka disease, Korin fever, Nidoko disease

Definition. Epidemic hemorrhagic fever is an acute infectious dis ease of still unproved etiology that is characterized by fever, purpura peripheral vascular collapse and acute renal failure

Distribution The disease has been recognized in the Amur River basin of Siberia and Manchuria since 1935 It first appeared among United Nations forces in Korea in the summer of 1951 (Fig IX 1)

Other hemorrhagic fevers of Western Siberia, European Russia and the Balkans appear to be different entities

Etiology. It has been established that the etiologic agent is fil trable that it is transmissible by inoculation of blood, urine, or tissues obtained early in the disease, and that neutralizing antibodies appear in the serum in convalescence There is evidence to suggest that the agent is maintained as a natural infection of field rodents and is spread to man by mites or chiggers No susceptible experimental animal has been found

Epidemiology. The lack of a susceptible laboratory animal and of a specific diagnostic laboratory test limits epidemiologic study, since dependence must be placed on those human infections which are recog nizable clinically The disease occurs throughout the year in certain



Figure IX.1 Geographic distribution of epidemic hemorrhagic fever (Courtesy Office of the Surgeon General Dept of the Army TB Med 240)

endemic foci, with two distinct peaks of incidence—one in May June the other in October-November (Fig IX 2) The disease occurs in rural environments, and 90 per cent of infections are isolated events as regards time, place and person The remaining 10 per cent however, consists of sharply defined outbreaks limited to a company, platoon or squad In such instances it is possible to trace the exposure to a limited time and a geographic focus

Previous studies strongly support the concept that trombiculid mites are probably the vectors The disease is not communicable from person to person by ordinary contacts

With cessation of active military operations in Korea only occasional instances of the disease are seen in United Nations forces With resettlement of certain of the endemic areas small outbreaks of the disease were noted in native Koreans but these also have ceased

Pathology. Three fourths of all deaths occur within the first ten days of the disease Shock is the most common cause of death, particularly in the early period although not limited to it Later in the disease, acute renal failure, hemorrhage into vital centers, or pulmonary

edema are also responsible for a fatal outcome The basic morphologic

or frankly hemorrhagic Necrosis in the same region varies from involvement of the tubular epithelium only to extensive necrosis of all pyramids The heart characteristically shows a hemorrhagic right atrium, focal myocarditis and cellular infiltration of the endocardium Focal necrosis is common in the anterior pituitary and adrenal glands Retroperitoneal edema is marked early but disappears later in the disease Edema of areolar tissue, particularly in the retroperitoneum, is striking early in the disease

Clinical Characteristics. The incubation period is usually about 14 days, with extremes of nine days to five weeks The disease varies widely in its severity, the greater number of cases taking the form of a mild febrile illness with proteinuria and minimal symptoms of infection One-fourth of clinically recognized cases can be classed as moderate or severe, and in these the progression of symptoms is relatively uniform For descriptive purposes this relatively typical clinical picture may be divided into phases each arbitrarily named for an obvious clinical feature Although such phases are recognizable, in their progressive appearance there is often some degree of overlap

Febrile Phase The onset is acute, with fever, anorexia, thirst and malaise The temperature rises rapidly to 103 to 105° F, persists for three to seven days, and usually falls by rapid lysis about the sixth

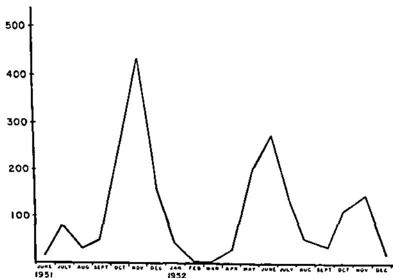


Figure IX.2 Hospitalized cases of epidemic hemorrhagic fever in United Nations forces in Korea 1951–52 (Courtesy Office of the Surgeon General, Dept of the Army TB Med 240)

day During this period there is often a distinct flush of the face and neck the throat is similarly flushed but *not* sore and the conjunctivae are suffused *Evidence of increased capillary* permeability or frank leakage of plasma may be manifested by chemosis periorbital edema and proteinuria Abdominal or lumbar pain may possibly indicate developing retroperitoneal edema Petechiae may be found in the axillary folds the conjunctivae or elsewhere and their appearance is thought to reflect varying degrees of trauma Hematuria is common *Rumpel Leedes test* is positive and thrombocytopenia may be present The blood count which earlier was normal or slightly leukopenic often shows a leukemoid *leukocytosis by the third day* Hemoconcentration results from the capillary leakage and is manifested by a rising hematocrit

Hypotensive Phase At the time of defervescence hypotension appears In severe cases faintness anxiety and apprehension are signals of the approach of medical shock in which the pulse may rapidly become imperceptible and the blood *pressure undemonstrable The finding of* warm extremities indicating arteriolar dilatation suggests that this picture is a composite of the pre existing hypovolemia from plasma leakage and a collapse of peripheral resistance This period characterized chiefly by hypotension lasts from several hours to a few days Shock merges with the phase of renal failure but is not established as a causal factor

Renal Failure Phase Hematuria continues proteinuria is pronounced and even in the absence of preceding shock some signs of renal failure appear heralded by a diminishing urinary output and rising levels of nitrogenous products in the blood The degree to which each of *these basic functions is impaired is variable and not necessarily* parallel Oliguria of some degree is common in severe cases and even anuria may develop Mild azotemia or severe uremia may be seen During this oliguric period hypotension disappears arterioles apparently regain thir tone capillary leakage ceases extravasated plasma returns to the vascular compartment and the elevated hematocrit falls Apparently the dilated capillary channels which were packed with erythrocytes during the period of shock do not rapidly return to a functional state *The restoration of blood volume combined with the reduced capillary* space produces a "relative hypervolemia"

At this time blood pressure rises sometimes to hypertensive levels peripheral veins are distended despite normal venous pressure circulation time is reduced but renal plasma flow is diminished hemorrhages become more frequent or marked and symptoms appear which are ascribed by some to relative hypervolemia" and considered by others to be typical of uremia Furthermore there appears to be a hemodynamic *inflexibility* in which minor variations in fluid balance result in pulmonary edema or dehydration and shock

Recovery Phase Following a one to five day period of mild or marked urinary *suppression diuresis occurs Concomitantly* capillaries obstructed by sequestered red cell masses are cleared There follows a relatively rapid readjustment of hemodynamics fluid balance electrolyte equilibrium and azotemia Urinary excretion *may reach 6 or even 8*

liters per day but the specific gravity remains low indicative of residual impairment of tubular function

Convalescence Symptoms and signs rapidly disappear except polyuria and concentrating functions of the kidney return more slowly to normal over the next few weeks Residua are rarely seen and long term sequelae are unknown

Diagnosis The diagnosis is suspected with the acute onset of a high fever in a person who has been exposed to rural conditions in a known endemic area No single early finding is diagnostic but the appearance of the flush petechiae hematuria proteinuria and leukemoid leukocytosis offer strong supporting evidence Progressive defervescence shock and renal failure in the absence of other obvious causes establish the diagnosis

Differential Diagnosis At various stages before the full progression of the disease is apparent it may be confused with leukemia thrombocytopenic purpura infectious mononucleosis leptospirosis acute glomerulonephritis scarlet fever the typhus fevers encephalitis purpura variolosa and an acute surgical abdomen

Prognosis With close observation and sound supportive care the case fatality rate can be held to 5 per cent Recovery is usually rapid and apparently complete although rarely a patient may show evidence of persistent renal tubular damage Sequelae are unknown

Treatment No specific chemotherapeutic agent is known to date Sulfonamides antibiotics vitamins antihistaminics pituitary and adrenal hormones convalescent serum and whole blood have had little or no effect on the course of the disease At present treatment is primarily supportive as follows

1 *Early hospitalization* is recommended since the severity of the disease cannot be prophesied on the basis of early symptoms The tendency toward hemorrhage and shock is reduced by gentle handling avoidance of trauma and physical activity and institution of early bed rest

2 *Maintenance of fluid balance* must begin early to avoid the overhydration which can result from the patient s attempts to satisfy the thirst which is prominent early in the disease In fact if hospitalization is delayed and careful intake output records have not been kept it is often wise to allow only minimal fluid requirements Until convalescence begins it is of prime importance to set fluid requirements on the basis of the volume lost in urine and vomitus plus an allowance of 500 to 700 ml per day for insensible loss The maintenance of fluid

avoided When intravenous administration of fluid is required because of severe nausea and vomiting 5 per cent dextrose is recommended Saline solutions are contraindicated because of their potential oncotic effect

3 *Hypotension* must be watched for by recording periodic blood pressure readings early in the disease in order to avoid the insidious and often sudden appearance of severe shock Mild degrees of medical shock may be handled by the simple but effective measures of the Trendelen burg position and elastic bandaging of the extremities If shock is more severe, continuous intravenous pressor therapy is usually required For this purpose *l* arterenol (l norepinephrine, Levophed) is the drug of choice, and administration in 5 per cent glucose using an indwelling catheter in the femoral vein is recommended The diastolic pressure should not be raised to 90 mm of mercury or above, since such pressures result in reduced blood flow through the kidney When plasma volume has been greatly reduced as indicated by hematocrit levels above 55 to 60 per cent the administration of salt free albumin is indicated After capillary leakage has ceased, albumin probably serves no useful purpose and may even be harmful With the hypertension of the late renal phase a phlebotomy of 500 ml may be effective in relieving the uremic or hypervolemic" symptoms particularly if improvement has been noted on a preceding trial of bloodless phlebotomy using pneumatic cuffs about the extremities

4 *Electrolyte imbalance* must be corrected where possible by re placement of deficits Cautious administration of insulin and 5 per cent dextrose in water may alleviate hypercalcemia, retention enemas of cation exchange resin have also been useful, but care must be taken to avoid inspissation and impaction in dehydrated patients

5 *Sedation* is effective in allaying or reducing many of the symp toms which disturb the patient or aggravate the physiologic imbalance Barbiturates may be sufficient but there should be no hesitation to employ meperidine hydrochloride (Demerol) if required In the presence of severe shock and impaired circulation repeated intravenous doses of 10 mgm of this drug are more effective than larger doses by other routes and are less likely to result in overdosage

6 Close *medical observation* and good nursing care are essential

7 *Ambulation* during convalescence should be based on return of renal tubular function as determined by concentration tests When a concentration to 1 012 is reached bathroom privileges are permitted free ambulation on the ward is allowed with a concentrating power of 1 014, and full activity when specific gravity reaches 1 023

Prophylaxis and Control In view of the suggested implication of trombiculid mites as vectors of the disease, the control measures ap plicable to scrub typhus are advisable These methods include impreg nation of clothing with miticides use of insect repellents on exposed body surfaces, rodent control measures and burning or bulldozing of camp sites (see Table XI 10, pages 772–778)

62

Bartonellosis

Synonyms. Verruga peruana, Oroya fever, Carrión's disease, en fermedad de Carrión

Definition. Bartonellosis is a specific infection caused by *Bartonella bacilliformis*, presenting two clinical types of disease The severe form, Oroya fever, is characterized by fever, a rapidly developing, macrocytic anemia, and frequently intercurrent infection with high mortality The cutaneous form, verruga peruana, is characterized by a verrucous eruption of hemangioma-like nodules and by a negligible mortality

Distribution. The disease is restricted to the western portion of South America between latitudes 2° North and 13° South, occurring especially in Peru, Ecuador and Colombia Its distribution is further restricted to narrow river valleys and canyons at altitudes between 800 and 3000 meters above sea level It has been reported from both sides of the Andes

Etiology. *Bartonella bacilliformis* is a minute gram-negative, rod shaped or rounded organism found in varying numbers within both the red blood cells and cells of the reticuloendothelial system especially those of the lymph nodes, spleen, liver, and kidney In the past there has been divergence of opinion with respect to the classification of these intracellular bodies This genus is now considered as standing apart from true bacteria, rickettsiae and filtrable viruses

In stained preparations of blood, both rod shaped and rounded forms are seen The rods are often slightly curved, occurring singly or end to end in pairs or in chains Frequently they lie parallel or are arranged in V's or Y's The rod forms when stained by Giemsa s method commonly show a deep red or purplish granule at one end suggestive of chromatin, the remainder taking a bluish stain (Fig IX 4)

They may be cultivated best in semisolid nutrient agar containing 10 per cent rabbit serum and 0 5 per cent rabbit hemoglobin

Epidemiology. The disease is endemic in certain arid river valleys of the Andes region and is coextensive with the distribution of the sandflies, *Phlebotomus noguchii* and *P verrucarum* in Peru However, the former does not bite humans and only rarely enters houses At the present time only *P verrucarum* has been incriminated as a vector Other species are reported from the endemic areas in Colombia The disease is especially prevalent at the close of the rainy season when these flies are most numerous

Proboscis infections with *Bartonella* have been found in wild-caught

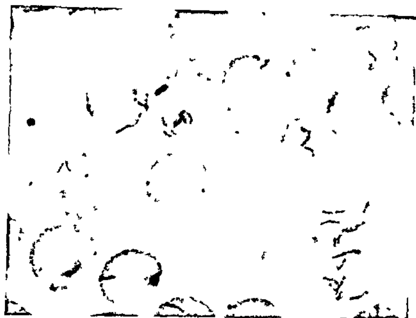


Figure IX.4 *Bartonella bacilliformis* in stained blood film.

to appear in successive crops Scarring varies with the extent of tissue destruction

Diagnosis The strictly limited geographic distribution and the distinctive clinical features of the infection almost eliminate any diagnostic difficulties Definitive diagnosis depends upon the demonstration of *Bartonella* in Giemsa stained blood films or on culture (Fig IX.4)

Treatment *Patients with acute bartonellosis show dramatic clinical* response when treated with penicillin streptomycin chloramphenicol or the tetracyclines Fever disappears in four to eight hours or less and the organisms diminish markedly Even though satisfactory clinical response is obtained the patient may continue to have positive blood cultures and develop verrugas but he will not die of the disease Presumably the antibiotics control the acute infection and allow low grade infection and the development of a protective immunity The choice of an antimicrobial drug should depend on the presence of secondary bacterial infection Transfusions of whole blood are recommended for symptomatic relief of the acute anemia

After the development of cutaneous lesions the response to antibiotic therapy is minimal Excision of the large necrotic secondarily infected nodules may be indicated

Prophylaxis The prophylaxis of bartonellosis consists of control of or protection against *Phlebotomus* Residual spraying of buildings and adjacent potential breeding areas with 5 per cent DDT in kerosene gives excellent results which persist for *several months Temporary* individual protection may be obtained by the use of insect repellents (p 772)

63

Tropical Ulcer

John P O Brien

Synonyms Ulcus tropicum Naga sore, tropical sloughing phagedena

Definition A chronic often progressive sloughing ulcer, usually occurring on the lower extremities It may extend deeply with destruction of underlying muscles tendons periosteum and bone Numerous spirochetes and fusiform bacilli as well as other bacteria are generally present in the lesions

Distribution It is widespread throughout the tropical areas of the world and is particularly prevalent in the wet tropics

Etiology Tropical ulcer is a clinical entity of uncertain etiology Spirochetes and fusiform bacilli are often present in the developing lesion It is improbable that they can penetrate the unbroken skin The ulcer commonly develops at the site of an injury or abrasion

Both the spirochetes and the fusiform bacilli are obligate anaerobes which can be cultivated on artificial media The spirochetes which are morphologically identical with *Borrelia vincenti* are slender and delicate and present a variable number of shallow irregular turns *Fusobacterium fusiforme* is a coarse plump banded or beaded gram negative rod with tapered ends

Other bacteria which may be present include staphylococci streptococci and various gram negative organisms

Recent studies indicate that malnutrition especially deficiency of protein and vitamins may be important in the etiology of tropical ulcer and that the infection is due to low resistance

Pathology The pathologic change in tropical ulcer is essentially a necrosis of the skin and subcutaneous tissues in which many microorganisms are demonstrable The process tends to extend by continuity to adjacent structures The walls and base are composed of infected indolent granulation tissue in chronic cases bounded by dense fibrous scar (Fig IX 5) Squamous cell carcinoma may arise as a rare complication

Clinical Characteristics Tropical ulcer may occasionally develop in the absence of visible abrasion of the skin In such instances it is preceded by vesicle formation or it may appear first as an inflamed papule which breaks down to produce a rapidly extending phagedenic ulcer

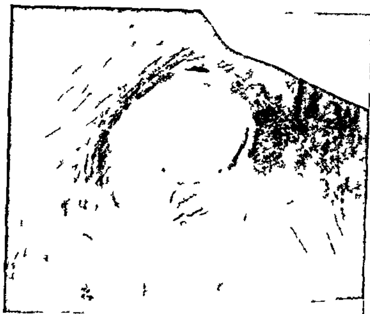


Figure IX 5 Tropical ulcer (Courtesy of Dr Hardy A Kemp Veterans Administration.)

The process may be associated with pain fever and toxemia In most instances it enlarges rapidly and may reach a diameter of 5 to 10 cm The base of the ulcer is composed of necrotic tissue and unhealthy granulations The edges are not greatly indurated or raised but may be undermined It is commonly attended by marked disability

Diagnosis Laboratory examination is required to exclude cutaneous diphtheria oriental sore and other specific ulcerations such as those due to *Mycobacterium ulcerans* and blood dyscrasias

Treatment. General measures particularly complete bed rest and a full diet are important Specific treatment falls into two phases (1) the control of infection and (2) the subsequent promotion of healing

For the control of infection large intramuscular doses of penicillin combined with local mild antiseptic dressings such as a 1/1000 aqueous solution of acriflavine should be used The local application of penicillin is not recommended Neomycin bacitracin and Aureomycin are of value locally but it is doubtful whether they have any advantage over cheaper antiseptics

When gross infection is controlled the ulcer should be covered with soft paraffin gauze and the parts immobilized by a plaster of paris cast or less effectively by adhesive tape. Skin grafting by "split skin" grafts is of great value and if used should be combined with immobilization

Prophylaxis Prophylaxis against tropical ulcer consists of cleanliness of the skin adequate protection against minor injuries early and proper treatment of minor trauma such as scratches small abrasions or insect bites and subsistence upon an adequately balanced diet

64

Tropical Eosinophilia

Synonyms. *Pseudotuberculosis of the lung with massive eosinophilia, eosinophilic lung, pulmonary eosinophilia, benign eosinophilic leukemia, eosinophilia with pulmonary disease, tropical eosinophilic asthma Frimodt Moller's disease, Weingarten's syndrome*

Definition. Tropical eosinophilia was first described in India among patients diagnosed as having tuberculosis Many of these patients, after thorough examination, were found to be free of tuberculosis but were suffering from a pseudotuberculous condition associated with massive eosinophilia Routine blood counts of all patients showed some with high eosinophilia varying from 20 to 90 per cent The condition is characterized by spasmodic bronchitis, leukocytosis and eosinophilia

Distribution. The condition is found in India, Ceylon, northwest and central Africa, Tanganyika, China the Philippines, Samoa, the Malay Peninsula, southern United States and a few other areas

Etiology. The true etiology of tropical eosinophilia remains obscure Recent studies have suggested that it may be caused by a virus which infects groups or families in close association The syndrome is found mainly in people who live by the sea It is thought by some to be a form of allergy The occurrence of positive complement fixation and skin tests using extracts of *Dirofilaria immitis*, the dog heartworm, as antigen and the therapeutic response to Hetrazan have suggested the possibility that filariae or other nematodes of animals occurring aberrantly in the lungs may well be involved etiologically in some cases of tropical eosinophilia

Pathology. The histopathology of this disease is still not clear, since it has caused directly few if any deaths The pathology is essentially eosinophilic bronchitis and bronchiolitis The most striking lesions

sic triad of cough, labored respiration and constitutional debility The typical patient presents a picture so characteristic that a diagnosis may be made clinically and later confirmed by blood analysis The physical signs are those of bronchial asthma The disease is characterized by paroxysmal cough, worse at night, with occasional hemoptysis Breathlessness is a major complaint and it varies from shortness of breath with

a sense of suffocation following bouts of coughing to expiratory dyspnea Other symptoms are fatigue pain in the chest and occasional night sweats The most striking feature is massive eosinophilia Patients with tropical eosinophilia that is left untreated usually have frequent remissions

The x ray picture of the chest shows enlarged hilar shadows and mottling in both lung fields The radiologic appearance resembles miliary tuberculosis but differs in the distribution of the mottled shadows These shadows also lack the clearcut and dense appearance of miliary tuberculosis

The disease occurs seasonally is found more often in men than women and is most frequent in persons between the ages of 20 and 30 It is usually benign and may last for years

Treatment The successful treatment by neoarsphenamine was discovered accidentally when a patient with concurrent syphilis was being treated Adequate treatment with organic arsenicals results in cure Carbarsone has been found to be as effective as any of the other arsenicals

Diethylcarbamazine (Hetrazan) has also been found to be an effective therapeutic agent This drug given at a dosage of 12 mgm /kg over a period of four days results in rapid improvement beginning on the second or third day There is also a prompt drop in the eosinophil count and marked improvement of symptoms

65

Desert Sore

John P O Brien

Synonyms Veld sore Barcoo rot

Definition This is a form of ulcer of uncertain etiology occurring usually on the face dorsum of the hands and forearms or on the lower extremities Its relationship to tropical ulcer is not established

Distribution It occurs in various desert regions of Australia Africa and the Near East

Etiology Lack of personal cleanliness local trauma and infection are important Desert sore is often associated with impetigo of the face and is considered to be related to this condition as well as to ecthyma The lesion characteristically develops at the site of a scratch an insect bite or an abrasion Staphylococci or streptococci or both are frequently present The role of diet is unknown

Pathology and Clinical Characteristics. Desert sore begins as a small vesicle containing thin seropus surrounded by a narrow zone of hyperemia The vesicle extends rapidly to a diameter of 1 to 3 cm, and after rupture of the roof a purulent ulcer is revealed Undermining of the edges with burrowing of the infection leads to irregularity of shape The edge
may
dry

In the *acute* stage the lesion is frequently painful and tender and it may be accompanied by regional adenitis, slight fever and malaise Complete healing may require a period varying from weeks to months A pigmented scar remains

The condition may spread rapidly among troops under desert conditions

Diagnosis. Desert sore must be distinguished from oriental sore, cutaneous diphtheria and tropical ulcer It differs from the latter in being more superficial and more purulent, and in the absence of phagedenic sloughing

Treatment. The treatment of desert sore is similar to that of tropical ulcer Antibiotic sensitivity tests may be required in the case of staphylococcal ulcers

66

Granuloma Inguinale

Synonyms. Granuloma venereum, granuloma pudente tropicum, chronic venereal sore

Definition. Granuloma inguinale is usually a venereal infection characterized by destructive, granulomatous, ulcerated and painful lesions generally involving the pudenda and adjacent tissues Occasionally invasion of the lymphatics and the blood stream produces metastatic foci accompanied by serious systemic disturbances which may result in marked destruction of the genital organs and spread to other parts of the body There is little tendency to spontaneous healing

Distribution. The disease is widespread in the tropics of Africa, the West Indies South America, the Pacific Islands, New Guinea north Australia, southern China and India It is not uncommon among Negroes

encapsulated bacillus, *Dono*
occurs intracellularly in large



Figure IX.6

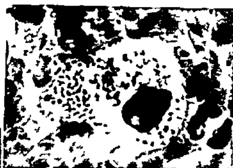


Figure IX.7

Figure IX.6 Granuloma inguinale Donovan bodies in large mononuclear phagocytic cell in stained smear from lesion. (Courtesy of Dr Donald C. A Butts)

Figure IX.7 Biopsy of lesion *Donovan bodies in large mononuclear phagocytic cell.* (Courtesy of Dr Donald C A. Butts)

mononuclear phagocytic cells and is constantly present in the lesions It *can be cultivated only in* embryonated eggs or embryonic yolk medium Isolated capsular material gives positive precipitin tests and fixes complement with sera of patients suffering from the disease (Figs IX 6 IX 7)

Epidemiology Granuloma inguinale occurs in both sexes but is more common in men It has not been observed before puberty and appears predominantly between the ages of 20 to 40 years Transmission is apparently by sexual contact

Pathology The pathologic changes are essentially those of a granulomatous lesion of the skin with superficial ulceration extending by continuity to adjacent areas especially on the genitalia the groins and the thighs Although the disease is usually restricted to the genital region involvement of the face mouth nose neck back and legs has been reported In these regions it is probably the result of autoinoculation or metastasis Metastatic lesions may occur in the bones or internal organs *Healing is accompanied by extensive fibrosis*

Histopathologic examination reveals a prominent round-cell infiltration of the corium with swelling degeneration and ultimate disappearance of normal connective tissue elements A surrounding infiltration of polymorphonuclear leukocytes lymphoid and plasma *cells and reticuloendo*thelial cells occurs Many swollen mononuclear phagocytes containing numerous Donovan bodies are present in the lesion There is marked formation of new connective tissue in which focal areas of inflammation and necrosis are commonly seen

Clinical Characteristics The incubation period is variable extending from a few days to two to three months The initial lesion may be a vesicle papule or nodule commonly on the penis of the labia minora This becomes eroded and superficially ulcerated with new nodule *formation* at the periphery as the lesion extends

In severe cases there may be extensive superficial destruction of the genitalia and the skin of the groins and thighs Severe involvement of

the vagina is followed occasionally by rectovaginal fistula Concurrently with extension of the process there is marked scar tissue formation and epithelization often presenting areas of secondary involvement and break down (Fig IX 8)

Diagnosis The diagnosis is based upon demonstration of the characteristic Donovan bodies These are found within large mononuclear phagocytes in smears of scrapings from the margins of the lesions stained by Wright s or Giemsa s stains A long and careful search may be required to detect the diagnostic forms in some cases



Figure IX 8 Granuloma inguinale involvement of skin of inguinal reg on (Courtesy of Dr Donald C A Butts)

Treatment Streptomycin is the drug of choice It should be given intramuscularly for a period of five to ten days depending upon the severity of the case Marked relief of pain may be expected within 24 to 48 hours accompanied by evidence of healing *Dosage* 4 grams da ly in divided doses administered intramuscularly every four hours While toxic effects are uncommon they should be watched for particularly evidence of eighth cranial nerve involvement

Aureomycin likewise has given good results and has proved useful in streptomycin resistant cases minimal dosage 250 mgm four times daily

Chloramphenicol (Chloromycetin) also is effective It should be given by mouth in divided doses of 250 mgm each for a total of 20 grams in the course of five to ten days

Intensive antimony therapy has been w dely used but is not to be recommended because of the limited margin of safety between therapeutic and toxic doses Although the antimonials cause regression of the disease and healing of the lesions in many instances treatment must be prolonged Lithium antimony thiomalate (Anthiomaline) and stibophen

(Fuadin) are preferred because of their greater stability and lesser toxic ity Dosage Anthiomaline should be administered intramuscularly in doses of 3 ml six times a week for four weeks Fuadin likewise should be administered intramuscularly daily or three times a week for a total of 40 ml of the solution The recommended initial dose is 1 5 ml the second 3 0 ml and subsequent doses 5 0 ml

Local treatment of the lesion with podophyllin for five to seven days has given dramatic results It is usually followed by prompt healing as in any simple uncomplicated ulcer As originally used a 20 per cent sus pension of the resin in olive oil is smeared gently over the lesions once or twice daily This commonly produces a secondary inflammatory process with pronounced local pain Much of the irritation is avoidable if a var nish composed of a suspension of the resin in compound tincture of benzoin is substituted for the olive oil suspension and if surrounding skin areas are protected by petroleum jelly In either case secondary bacterial infection should be reduced to a minimum before the institution of podophyllin therapy

67

Effects of Heat

John P O Brien

Physiology of Heat Regulation

Body temperature is the resultant of the rates of heat production within the body and of heat loss by the body These processes are con trolled by the nervous system the main center being in the hypothal amus Exposure to high environmental temperature initiates a combina tion of physiologic processes serving to increase the dissipation of heat through physical mechanisms The relative importance and effectiveness of each of these mechanisms is determined in part by the relative hu midity

Loss of heat by radiation convection and conduction is the most im portant of these mechanisms (Table IX 1) The quantity of heat elim inated varies with such factors as the environmental temperature rela tive humidity clothing and the rate of heat production Increased loss by radiation from the body surface is accomplished by cutaneous vasodila tation and increased blood volume and circulation rate Loss by conduc tion varies inversely with the amount of subcutaneous fat Further dis sipation of heat is accomplished by convection currents created between

Table IX.1. Physical Mechanisms of Heat Loss from the Body at Ordinary Temperatures*

	PERCENTAGE OF
Urine and feces (heat of these excreta over that of food and water)	2
Total daily heat loss	100

* Adapted from Best C H and Taylor N B The Physiologic Basis of Medical Practice Baltimore, Williams & Wilkins 1955

the layer of warm, moisture laden air in contact with the clothed body and the surrounding atmosphere when the latter is cool and dry

when the environmental tem-
When the relative humidity is
of sweat is reduced to a mini
mum

Significant amounts of heat are dissipated through the evaporation of sweat secreted from the skin Sweat is a weak solution of sodium chloride varying in concentration from 0 2 to 0 5 per cent and containing traces of urea and inorganic salts A rise in blood temperature acts upon the nervous centers, providing the normal stimulus to perspire Heavy muscular work and profuse sweating over a prolonged period increase the

and tissue fluids An actual fall in sweat production occurs with prolonged exposure to intense heat, and the fall is progressive and steep when the blood temperature rises above 100 to 101° F In man, heat loss by evaporation is not effective in the lungs

Physiologic Response to Heat

The physiologic responses to exposure to high temperature are vaso dilatation acceleration of the pulse and respiration, profuse sweating, and a reduced capacity for muscular work Acclimatization to hot environments is essentially an adaptation of the heat regulating mechanisms One of the most important features of acclimatization is the development of an increased capacity for sweating without undue loss of sodium chloride In most individuals this adjustment is fairly well established within one week and is effected mainly by the adrenal cortex

Effects of Heat

The ill effects of heat are expressions or resultants of the excessive loss of chlorides and water and of failure of the heat regulatory mechanisms The clinical syndromes are not sharply defined, intermediate and mixed types are frequent The principal syndromes have been designated as (1) heat stroke, (2) heat cramps, (3) heat exhaustion and (4) anhidrotic

asthenia (anhidrotic heat exhaustion) Miliaria rubra and sunburn are minor effects Psychologic effects are not discussed here

Heat Stroke

Synonyms Heat pyrexia sunstroke heat hyperpyrexia thermic fever sun traumatism siriasis

Definition Heat stroke is a response to exposure to excessive heat and humidity characterized by high fever circulatory collapse and in severe cases coma convulsions and death It probably arises from a fatigue or failure of the central nervous heat regulating mechanism and sweat glands After recovery from the acute episode a fairly prolonged period of instability of the heat control mechanism is usual In some instances there is permanent loss of ability to adapt to high temperature and humidity

Etiology *Heat stroke usually occurs after prolonged exposure to* an excessively high temperature often accompanied by high humidity and lack of air movement Predisposing factors are hard physical work heavy tight clothing and lack of ventilation It may be precipitated by heat exhaustion or anhidrotic asthenia Alcohol is an important immediate cause Cessation of sweating often precedes the onset

Pathology. Although there are no specific lesions edema conges*tion and petechial hemorrhages are often seen in the brain* meninges serous membranes heart and other viscera The upper intestine may be so severely congested as to create suspicion of poisoning

Microscopically the brain shows scattered areas of edema hemorrhage degeneration of neurons and where death is delayed *gliosis Com*parable pathologic changes are found in the heart liver kidneys adrenals and lungs

Clinical Characteristics Diminution or cessation of sweating and frequency of micturition may occur some hours in advance of the acute attack and constitute important warning signals Other prodromes are weakness lassitude headache vertigo anorexia nausea and increase of *body temperature and pulse rate* Muscle cramps may occur

The onset is often sudden with vomiting precordial distress muscular twitchings and anxiety or even mental derangement The patient is flushed the skin is hot and dry the peripheral vessels are distended

giving ... the
blood ... the
early s ... is a
... elir
Convulsions
us import
ted Cheyne

Stokes respiration may be present, and the tendon reflexes are usually diminished or absent The pulse gradually becomes weak and irregular, the blood pressure falls, and significant grades of dehydration may be encountered The urine output is diminished or there may be anuria, the chloride content of the urine may be markedly reduced Moderate amounts of albumin are present The spinal fluid is clear and under in creased pressure Temperatures above 108° F may induce irreversible changes in the brain

When recovery begins the temperature falls rapidly, resumption of

normally susceptible to heat

Diagnosis. The differential diagnosis from the hyperpyrexial form

Treatment. Intensive treatment should be initiated immediately

e
er cooled
massaged
ten min

utes and, when the temperature drops to 102 to 103° F the patient is removed to a bed and covered lightly Excessive cooling in or out of the bath, is a real danger Care must be taken to read the correct body tem perature, uninfluenced by water or environment Rather than a cool bath some prefer to cover the naked patient with a wet sheet and fan him vigorously This is not as effective when the humidity is high but may suffice for mild cases

and atropine are contraindicated The role of spinal fluid drainage is not established After termination of the acute phase, absolute rest and protection against even moderate temperatures are required to prevent relapse

Prognosis. Heat stroke constitutes a serious threat to life The mortality rate ranges from 15 to 50 per cent The prognosis depends primarily upon the duration of the acute condition prior to treatment and is poor in the very young and old Cardiac and renal disease and chronic alcoholism minimize the chances of recovery

Heat Cramps

Synonyms Stoker's cramps miner's cramps fireman's cramps

Definition This condition is characterized by the development of *painful cramps of the skeletal muscles following* exertion in high temperatures

Etiology Under conditions of high environmental temperature sweating is *profuse and leads to the loss of much water and sodium* chloride When the subject replaces only the water through massive thirst there tends to arise a state of relative hypotonicity and lack of sodium chloride in the tissues In the case of certain muscles this leads to severe cramps

Clinical Characteristics. Typically the onset is gradual and is characterized by mild cramps in the extremities The cramps are usually symmetrically distributed and transitory but tend to recur at shorter intervals and with increasing severity gradually involving the major muscle groups of the extremities and abdominal wall They are disabling and frequently extremely painful In severe cases they may recur for many hours unless checked by therapy

Treatment The administration of sodium chloride and water is specific In mild cases sodium chloride (1 gram with large fluid intake) should be given every hour for a total of 15 doses The salt should be given dissolved in water since tablets may cause vomiting In severe *cases sterile physiologic salt solution should be given intravenously* Symptomatic relief is rapid

Heat Exhaustion

Synonyms Heat prostration heat exhaustion type I salt deficiency heat exhaustion

Definition This is a type of response to excessive heat characterized by prostration and varying degrees of circulatory collapse accompanied by little if any rise in body temperature Simple fainting due to heat is called heat syncope

Etiology Under conditions of heat stress there tends to occur an excessive loss of water and sodium chloride from the body The sodium *chloride loss is particularly important* because imbibed water cannot be retained unless the tissues contain enough sodium chloride to maintain isotonicity

The progressive dehydration means lowered blood volume and a resultant shocklike form of circulatory collapse which is the chief feature of classic heat exhaustion In the aged and others with feeble hearts

cardiac failure may complicate the picture Associated heat cramps are common

Those who secrete much sodium chloride in their sweat are particularly prone to heat exhaustion

Clinical Characteristics. Warning symptoms over a period of two or three days are common These may consist of undefinable malaise and anxiety, or there may be in addition headache, vertigo, irritability, dim or disordered vision, shallow respiration, cramps, nausea and vomiting

The actual onset may occur during the night Heat exhaustion may appear in the course of other disease syndromes and may complicate surgery in the tropics, especially after lengthy procedures when the patient has been heavily draped

The clinical picture is predominantly that of shock with

1 Low blood pressure and syncope on standing The blood pressure while lying may be well maintained

2 Marked reduction of pulse pressure persisting as long as the diastolic pressure is readable

3 Oliguria

4 Marked reduction of urinary chlorides

5 Moderate elevation of rectal temperature, even though the mouth temperature may be normal or even subnormal

6 Profuse sweating and cold clammy skin

There is usually marked pallor, and if exposure to undue heat is continued, unconsciousness occurs and death follows from circulatory failure

Diagnosis. Heat exhaustion in the tropics must be differentiated from algid malaria food poisoning and chemical poisoning, which may produce an almost identical clinical picture

Treatment. In planning treatment it is well to keep in mind an important aphorism "Keep the exhaustion case warm, get the stroke case cool" The essential problem is the correction of the dehydration and salt deficiency and of the associated acute circulatory failure If the patient is conscious he should be pressed to drink cool water containing between 0 1 and 1 0 per cent sodium chloride concentrations at the upper range are more effective provided they do not cause vomiting In severe cases intravenous infusion of sterile physiologic sodium chloride solution (0 9 per cent) should be used but special care is required as regards volume and speed in treating those with organically diseased hearts Intragastric or rectal delivery of saline may be considered for unconscious patients when intravenous fluids are not available Fluid and electrolyte balance charts and blood chemistry studies are desirable Morphine is contraindicated

Prophylaxis (See page 624)

Anhidrotic Asthenia

Synonyms Anhidrotic heat exhaustion thermogenic anhidrosis heat exhaustion type II

Definition A recently recognized subacute disorder of heat control due to the blockage of many of the sweat glands of the body by miliaria rubra (*prickly heat*) It is the most common major heat disorder under military conditions in both the wet and dry tropics

Etiology The sweat glands involved by miliaria remain blocked for some weeks after the acute inflammation subsides When extensive blockage occurs physiologic adaptation to heat is disturbed Other causes of blockage are acute sunburn and diffuse skin diseases such as exfoliative dermatitis

Clinical Characteristics There is usually a history of severe or recurrent miliaria rubra some weeks before onset of general symptoms which characteristically take the form of excessive fatigue responses to physical exertion The patient notices over a period of a week or more that exercise in the heat of the day especially in sunshine causes exhaustion frontal headache giddiness dyspnea palpitation and in severe cases tremor and syncope With rest in the shade symptoms are largely relieved in one half to three hours In between periods of exercise a sense of well being is largely restored however there may be polyuria The disease lasts a few weeks and recovery then gradually takes place

Diagnosis Anhidrotic asthenia may be readily diagnosed by the following features *provided* the patient is examined after exertion

1 Relative or complete anhidrosis (absence of sweat) on the *covered* parts of the body

2 The presence of diffuse miliaria rubra or more often a *generalized* rash which although not related to the hairs looks like "gooseflesh (Fig IX 9) This rash called miliaria profunda (or mammillaria) and the associated anhidrosis are the cardinal signs Miliaria profunda is not red generally not pruritic and may disappear entirely on resting *In dry desert heat the whole syndrome may come on more acutely* while the skin is still at the miliaria rubra stage

3 *Excessive* sweating probably compensatory of the forehead and face Palms and soles sweat normally In the desert the anhidrosis may be more diffuse

4 *Marked tachycardia and tachypnea* and a slightly raised temperature (average rectal 100 to 101° F)

5 Features absent in typical cases hyperpyrexia dehydration salt deficiency cramps vomiting coma and immediate danger to *life*

Complications This disease is likely to precipitate a more acute heat disorder especially heat stroke

Treatment The patient should avoid exercise and be placed in a cool environment such as an air conditioned room *Evacuation from the tropics should rarely be necessary During recovery* exercise tolerance and sweat secretion should be checked regularly

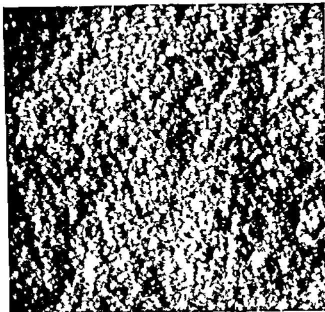


Figure IX.9 An enlarged picture of human skin showing miliaria profunda Notice the gooseflesh like appearance (Courtesy of Drs G O Horne and R H Mole Tr Roy Soc. Trop Med & Hyg 44 1951)

Local Treatment Inasmuch as the anhidrosis and miliaria profunda are due mainly to keratotic plugging of the pores restoration of sweating sometimes may be hastened if adequate desquamation can be brought about by repeated applications to the anhidrotic skin of 10 per cent salicylic acid in 70 per cent ethyl alcohol First paint a small area to detect any undue reaction Following desquamation inunction of lanolin cream should be used over the treated areas once a day Desquamation may need to be repeated

If as sometimes happens adequate desquamation cannot be brought about one must await the natural shedding of the obstructive plugs—this may take some weeks While ample inunction of lanolin cream may increase sweating (and exercise tolerance) during this period it is unwise to discharge the patient until sweating is normal without the use of lanolin

For treatment of acute miliaria rubra see below

Prophylaxis It is important to treat the miliaria rubra and to avoid sunburn

Synonyms. Prickly heat, miliaria heat rash, lichen tropicus.
Definition. Miliaria rubra is an acute inflammatory disorder of the skin associated primarily with blockage of the sweat pores. It is common throughout the hot, moist tropics.

Etiology. A large number of factors are now known to close the sweat pores. In the case of tropical miliaria rubra, the most important are probably maceration of the keratin of the stratum corneum and infection of the pores, especially by staphylococci (Fig IX 10A). Lipoid depletion of the stratum corneum may play an ancillary role.

Sudamina (crystallina or miliaria crystallina) is similar to miliaria rubra except that the blockage is more superficial and less prolonged. Many physical factors such as ultraviolet light (sunburn) may cause it.

Pathology. The changes appear to be entirely secondary to the pore blockage. Pressure built up through the continued secretion of sweat causes dilatation and finally rupture of the sweat ducts as they pass through the stratum malpighii. Vesicles containing sweat are thus produced in the malpighian layer (miliaria rubra) (Fig IX 10B). Congestion of dermal vessels and leukocytic infiltration occur.

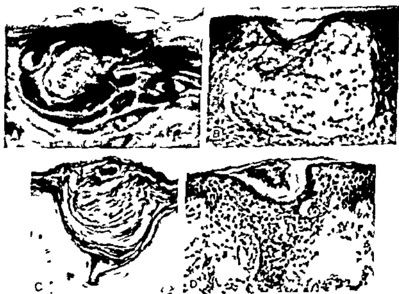


Figure IX.10 Stages in the development of miliaria. A Staphylococci in a pore (the large space slightly to the left of center) from a case of miliaria. This may be the earliest lesion. B Miliaria rubra showing the vesicle in the epidermis. The closed sweat pore is in the surface depression. C At a later stage a large darkly stained parakeratotic plug obstructs the sweat pore. D Miliaria profunda the final stage showing the parakeratotic plug on the surface and large empty spaces in the dermis representing extravasation of sweat. (Courtesy of Dr J P O'Brien in (A) J Invest Dermat 15 105 1950 (B and D) Brit J Dermat. & Syph 59 125 1947 (C) original.)

In the course of approximately ten days the acute vesicles disappear and a parakeratotic reaction with formation of a plug produces chronic obstruction This in turn leads to a deeper vesicle formation because the rupture of the ducts is in the dermis rather than the epidermis thus producing miliaria profunda (Figs IX 9 IX 10D)

The stage of acute vesiculation (miliaria rubra) is brief but the profunda stage is prolonged persisting for weeks Characteristically lesions in all stages of development coexist When all the pores of an area of skin are obstructed the area becomes completely dry (anhidrotic), and the lesions are for the most part in the chronic profunda stage

Clinical Characteristics The rash of miliaria rubra is largely confined to the clothed areas It consists of innumerable tiny vesicles on a red base and is accompanied by intense itching The early vesicles are succeeded by red papules and these in turn by the deep vesicles of the profunda stage These are not red not pruritic and resemble closely the white papules of "gooseflesh" (Fig IX 9)

Recurrent episodes of miliaria rubra represent progressive involvement of more and more gland groups Various pyodermas chronic dermatitis and anhidrotic asthenia are frequent sequelae

Treatment Exposure to a cool environment for even part of each day is of great benefit

The following antibacterial cream should be gently rubbed into the affected areas once a day in the morning

Neomycin sulfate	0 25
Cetomacrogol 1000 B P C	2
Mineral oil, light	6
Cetyl alcohol	10
Propylene glycol	2
Preservative (paraben type)	q s
Water	to 100

When irritation is very marked the neomycin may be increased to 0 5 per cent and hydrocortisone acetate added (0 5 to 1 0 per cent)

Between attacks the inunction of the following bland cream is useful in keeping the skin supple and in preventing lipoid depletion and poral closure

Lanette wax S X	3
Lanolin (anhyd)	5
Mineral oil light	2
Preservative (paraben type)	q s
Water	to 100

For treatment of miliaria profunda see treatment of anhidrotic asthenia (p 620)

Prophylaxis Clothing should be loose light clean and as brief as protection from the sun will allow Heavy continuous sweating should be avoided If facilities exist the spending of eight to 12 hours of each day in an air conditioned atmosphere is helpful Soap should be used only sparingly and a hexachlorophene soap may be recommended provided possible irritation from it is kept in mind Routine applications of powders is not desirable except in intertriginous areas such as the groin

Prophylaxis Against Effects of Heat

Prophylaxis against the acute effects of heat includes the maintenance of normal salt and water balances and avoidance of unnecessary exposure to conditions of high temperature and humidity Alcohol in a hot humid environment, especially prior to hard physical work, constitutes a serious menace The very young and the old are especially susceptible

Water requirements are subject to great variation, in the desert they may vary from two quarts to three gallons per day They are directly proportional to the environmental temperature and the amount of physical work performed At high temperatures a man at rest may lose one pint of water per hour Under extreme conditions total daily chloride needs may reach 30 grams The following essential rules should be observed

1 Working hours should be adjusted to permit the maximum amount of sleep Fatigue is a principal predisposing cause of acute effects of heat

2 Avoid unnecessary exposure to the sun, the head should be protected and clothing should be light and loose

3 Drink plentiful amounts of water containing 0 1 per cent sodium chloride Salt tablets (sugar or enteric coated) may be used in place of the saline, provided water intake is strictly maintained since even salt can be overdone A daily urinary volume of at least 900 ml should be achieved, and in special instances it may be advisable to watch for any changes in body weight and the chloride content of the urine

4 Take fluid, even in the absence of thirst or presence of nausea

5 Salt food plentifully

6 Rest in shade immediately upon the appearance of mild symptoms

7 Avoid and treat skin disease, especially miliaria Gradual suntanning is desirable, but acute sunburn is a hazard, as it may obstruct many sweat pores

8 Air conditioning facilities are of great value Evacuation from the tropics may sometimes be necessary as a prophylactic measure against recurrences

68

Certain Medically Important Animals

C Brooke Worth

The following discussion covers a miscellaneous group of animals which commonly injure man either mechanically or otherwise Except

for leeches and vampire bats, it does not include direct vectors of disease, since these are discussed elsewhere. A all categories are omitted for the same reason Echinode mentioned because of their relative unimportance as dire harm

No attempt is made here to furnish keys for the identific and snakes, rather, a few generalizations are offered cor recognition and treatment of injuries caused by the dange and the methods of protection against them

Coelenterates

Persons bathing in tropical or subtropical oceans occa be stung by a variety of marine animals, certain coelenterat commonest of such offending agents These organisms occ free swimming jellyfish (medusae) or as sessile polyps T semble plants, since they have stalked bodies and a flowe of tentacles, but they are true animal forms Both medusae possess tentacles which bear numerous tiny stinging struct tocysts) When a tentacle comes into contact with any or nematocyst discharges a small barb and a minute quantity the victim's cuticle or skin Man responds variably to the att ing on the number of stings sustained and the type of to There may be a mild local reaction or a profound systen stings of tropical species are more severe and may rarely re

Jellyfish often occur together in large numbers, having b close to land or washed ashore by storms and shifting oc in certain seasons It may then be wise to avoid sea bat wear shoes while walking along the beach Sessile polyps a of a menace and are annoying chiefly to divers

Clinical Characteristics. The Portuguese man of wa colonial coelenterate that floats by means of a brightly bladder The stringlike tentacles of this elaborate assembl dependent individuals stretch for many yards around engaging such a tentacle while swimming at once receives stings, and soon the exposed part shows a row of circular patches spaced a few millimeters apart where contact wi nematocysts was made

Local marks of the stings of jellyfish may be absent in Pain, swelling and redness of the affected part usually occ Systemic effects following severe stinging appear within a in a much briefer time, and may consist of anxiety, musc cramps, dyspnea, constriction of the throat, cardiac weakn tration Sensitive individuals may show an anaphylactoid typ in which cough, coryza and urticaria are outstanding

Treatment In untreated cases the systemic signs usually subside within a few hours or days although an itching dermatitis at the site of the stings may persist for weeks The intravenous injection of 10 ml of a 10 per cent solution of calcium gluconate has been found specific for the systemic disturbances Administration of Benadryl intravenously and epinephrine intramuscularly may be indicated in some cases Topical applications of weak alkaline solutions such as diluted household ammonia help relieve the cutaneous symptoms Local application of an analgesic ointment usually affords relief

Leeches

These animals have segmented bodies provided with anterior and posterior suckers used in locomotion and attachment At the center of the anterior sucker is the mouth which may possess cutting teeth In sucking blood leeches secrete an anticoagulant hirudin the action of which often continues even after the animals have engorged themselves and dropped off the host the lesions bleed for some time heal slowly and therefore may become infected

Most leeches inhabit fresh water although a few tropical species have adapted themselves to a moist terrestrial environment Land leeches are found in South America and in the Far East where they are especially troublesome in Malaya Assam Burma India Borneo and parts of the southwest Pacific They are most abundant during the monsoons They reach a human host from brush at the edges of overgrown trails or may climb up the host s legs from the ground quickly finding openings in clothing and gaining access to the skin Aquatic leeches affix themselves to bathers or reach the mouth in unfiltered drinking water

Clinical Characteristics. Leeches entering the mouth may migrate to the nasal cavity pharynx trachea or bronchi In such locations their subsequent engorgement leads to mechanical obstruction of the passages They may be removed by applying strong cocaine to their bodies after the patient has been placed with his head in a lowered position to prevent deeper penetration of the respiratory tract by the dislodged parasites

Invasion of the urethra and bladder is also known and may be overcome by irrigations with strong salt solution Leeches reaching the stomach are digested

The bites of these animals are ordinarily either painless or felt only as a slight irritation Persons in areas inhabited by land leeches are sometimes unaware that they are carrying them Travelers occasionally become weakened to the point of exhaustion by loss of blood without knowing the cause of their condition until their clothing is removed and

a heavy infestation is discovered Exsanguination of animals due numerous bites has been observed and death in man resulting from t cause is alleged to have taken place on rare occasions

Ordinarily however land leeches are soon discovered by a hum victim This may proceed from the unpleasantness occasioned when inch long engorged leech is squashed inside a shoe At other times th blood staining of trouser legs resulting from continued bleeding afte leeches have fed and detached is an indication of the presence of thes animals Local guides may give warning of a leech infected forest before permitting travelers to enter In such a case many leeches can be removed before they have a chance to inflict their wounds or they may be dis lodged before completing engorgement

Many persons suffer no after effects from leech bites but those with sensitive skins or allergic tendencies may experience severe local itching for several days

Treatment A leech attached to the skin may sometimes be dis lodged by the simple expedient of pulling it off by hand Otherwise it can be induced to detach itself by applying cocaine vinegar table salt or other strong solutions to it Touching it with a lighted cigarette will also cause it to let go Oozing of blood should be controlled with a styptic pencil Secondary infection and ulceration may occur if the bites are neglected or if the mouthparts remain in the skin after removing the rest of the leech

Prophylaxis Several ordinary mosquito repellents (Indalone 612 and dimethyl phthalate) are fairly efficient in repelling leeches retaining their effectiveness against these animals long after the effect against mosquitoes has been lost Newer repellents hold promise of greater efficacy Clothing impregnated with repellents has also proved to be an effective prophylactic measure in tropical areas

Fishes

Species of both marine and fresh water fish may injure man by sharp spines which sometimes are associated with underlying poison glands The salt water varieties usually wound bathers who step on them for many of these forms habitually lie half buried in silt hidden under marine vegetation or in crevices of coral formations Sting rays are the most dangerous fish in this category and are found in shoals or bays with sluggish currents and muddy or sandy bottoms Such elasmobranchs may be very large and possess long slender lashing tails near the base of which one or more stout barbed spines are situated These are dorsal fin rays often associated with poison glands although it has been said that a coating of mucus is the chief agent responsible for the toxic effects of the sting Rays are especially abundant in Australian and Asiatic

are most frequent on the ankle the barb sometimes being driven to the bone

In the Pacific Ocean stone and scorpion fishes are found on coral reefs These bony fish have poison spines whose effect may be very severe The toad fishes of the American tropics are similarly dangerous These forms may all be easily recognized by their very spiny appearance

Fresh waters in the tropics especially the Amazon also may harbor sting rays as well as large catfish bearing sharp spines Other species of catfish give painful wounds the world over They usually inflict their damage while being removed from fishhooks Poison glands are associated with the spines of many of these Puncture wounds produced by spiny fish are usually ragged and easily become secondarily infected

There are also biting fish some of which secrete poison The famous piranha of the Amazon and its tributaries is not venomous but is attracted in large schools to any wounded animal quickly tearing it to pieces Electric eels and rays represent another dangerous type of fish large specimens causing transient partial paralysis or possibly fatal shocks in man

Clinical Characteristics The most severe cases of poisoning due to the stings of venomous fish are confined chiefly to a few marine varieties There is an immediate painful reaction at the puncture site or sites followed rapidly by marked swelling and erythema Systemic effects may include dyspnea prostration or delirium Death has occurred rarely Immediate local treatment as for snake bite including incision and suction may be of aid in preventing or retarding the absorption of poison

The ingestion of spoiled fish containing bacterial toxins will not be considered Poisoning of man following the eating of certain fresh caught inherently poisonous marine fish has commonly been noted however This has occurred in many parts of the world and is known as ichthyosarcotoxism This refers to the ingestion of the flesh of poisonous fishes which are found in all warm seas and a few that are known from temperate latitudes The disease is an intoxication resulting from the ingestion of a neurotoxin found in the bodies of certain species of fishes Infections are manifested by symptoms of weakness myalgia pruritus malaise paresthesias of the mouth and extremities paralysis and convulsions When death occurs it is due to respiratory paralysis The chemical and pharmacologic properties of ichthyosarcotoxins are not known There are also seasonal variations in the edibility of certain species within a given region Poisonous species rarely if ever occur far at sea

Prophylaxis The best guide to safety in consuming fish is the example set by natives of each region If such local advice cannot be obtained one should avoid fish with leathery bristly spiny or tuberculated skin This will exclude the highly poisonous trigger fish puffer fish and porcupine fish The pufferfish inflates itself with air when caught Trigger fishes are brightly colored the anterior part of their

dorsal fin is modified as a spine resembling a trigger and there is a gap between this structure and the posterior unmodified part of th The "trigger" is situated far forward over the eyes Porcupine fishes long sharp bristles or spines over the head and back and smaller over the belly The parrot fish and red snapper normally scaled spec may likewise occasionally be poisonous Parrot fish have mouths sembling a parrot's beak

Evisceration preparatory to cooking should be done with meticulo care fish showing enlarged gonads had best be discarded since som species are inedible only during their breeding season Even so there i some danger in consuming unfamiliar species as not all the harmful varieties are excluded by the above criteria and the poison of dangerous forms is not destroyed by cooking it Unfamiliar fish eggs should never be eaten

Treatment Treatment in the early stages consists of gastric lavage or the administration of an emetic Later it is necessary to support the circulation if cardiac failure appears Deaths have been known to occur within two hours of eating unspoiled adequately cooked poisonous fish Although inherently poisonous fish exist all amphibians reptiles birds and mammals are edible and may be eaten with safety after thor ough cooking

Lizards

Lizards the world over are nonpoisonous except the gila monster of southern Arizona and New Mexico and the beaded lizard of southwestern Mexico Even these are rarely harmful since the venom secreted at the base of certain of their lower teeth does not readily enter the shallow wounds produced They do not often bite man but when they do they may maintain a firm grasp with their jaws and it is sometimes most difficult to dislodge them Their tendency to turn over on their backs when biting enables the venom to flow into the lacerations more readily Paralysis dyspnea convulsions and rarely death may result Local treat ment as for snake bite should be practiced for removal of the venom These reptiles may be recognized by their tuberculated skin stumpy ls and coloration Gila monsters are mottled salmon pink and black aining a size of about two feet The slightly larger Mexican beaded rd is yellow and black

Harmful snakes are widely distributed especially in warm parts of the world Large boas and pythons occur strictly within the tropics and while capable of injuring or killing man by biting and constriction are rarely encountered They are nonpoisonous The chief danger from snakes lies in the effects of bites by venomous species

Poisonous snakes occur in both the tropics and temperate regions In Tasmania all the snakes are poisonous and in the rest of Australia they outnumber the nonpoisonous fauna but elsewhere in the world they take a decidedly minor place both in number of species and in actual number of individuals In the Amazon valley, for example snakes are not numerous generally speaking and poisonous ones account for only 3 to 5 per cent of the total snake population Certain islands such as Hawaii New Zealand New Caledonia Ireland Madagascar and many others as well as the Arctic regions are entirely free of poisonous land dwelling snakes however tropical islands of the Pacific and Indian Oceans some of which are terrestrially snake free have sea snakes in their fringing surf The chief poisonous snakes of importance are listed in Table IX 2

Fangs Many venomous snakes possess fangs that are ill adapted for piercing the human skin This is especially true of the rear fanged colubrids whose fangs not only are set far back in the uppper jaw but also are merely grooved rather than hollow This means that venom poured from the duct of the venom gland at the base of the fang must flow along the groove to reach the surface of the wound In many front fanged snakes the duct leads directly into the hollow fang itself and venom may be ejected with force through the hypodermic needle like tooth deeply into the wound (Fig IX 11)

Front fanged snakes may have either of two types of fang movable or immovable The immovable type found in sea snakes and elapids is relatively less efficient since owing to its permanently erect position it must be short to permit closing of the jaws Moreover this type is invariably grooved rather than hollow Thus highly poisonous snakes such as cobras kraits coral snakes and all the Australian species are less effective in their attempts to bite Even cobras must sometimes chew their victims after striking them in order to introduce enough venom to end their struggles

The true vipers and the pit vipers have hollow front fangs solidly attached to movable premaxillary bones These complex structures are folded back against the roof of the mouth when not in use but are directed forward while the snake is striking This arrangement permits the fangs to attain greater length some large species have fangs so long that they can deliver their venom intramuscularly These snakes strike quickly and immediately withdraw to await the effect of their bites

The fangs of vipers and elapids when not in use are enclosed in a protective mucous membrane sheath In examining a specimen to detect

Table IX.2. Important Poisonous Snakes of the World

FAMILY AND TYPE OF FANGS	COMMON NAMES	TYPE OF VENOM	DISTRIBUTION	REMARKS
COLUBRIDAE rear immovable grooved	Colubrids	Mostly mild	Warm parts of both hemispheres	Over 1000 species, the few poisonous ones not dangerous
Example	Boomslang	Hemorrhagin	South Africa	Arboreal, timid
ELAPIDAE front immovable grooved	Elapids	Predominantly neurotoxin	Mostly in Old World	Over 150 species very poisonous
Examples	Cobras	Mostly neurotoxin	Africa, India, Asia, Philippines, Celebes	Spitting cobra in Africa aims at eyes
	Kraits	Strong neurotoxin	India, S.E. Asia, Indonesia	Sluggish, often buried in dust
	Mambas	Neurotoxin	Tropical W. Africa	Arboreal
	Blacksnake	Neurotoxin	Australia	Large snake, wet terrain
	Copperhead	Neurotoxin	Australia, Tasmania, Solomons	Damp environment
	Brown snake	Neurotoxin	Australia, New Guinea	Slender
	Tiger snake	Strong neurotoxin	Australia	Dry environment, aggressive, very dangerous
	Death adder	Neurotoxin	Australia, New Guinea	Sandy terrain
	Coral snakes	Neurotoxin	United States, tropical America	About 26 species, 2 in southern U.S.A.
HYDROPHIDAE front immovable hollow	Sea snakes	Some mild, others very toxic	Tropical Indian and Pacific Oceans	Gentle. Rudderlike tail. Over 50 species
VIPERIDAE front movable hollow	True vipers	Predominantly hematoxin	Entirely in Old World	About 50 species
Examples	European viper	Hematoxin	Europe (rare), N. Africa, Near East	Dry rocky country
	Russell's viper	Hematoxin	S.E. Asia, Java, Sumatra	Mostly open terrain, deadly
	Sand vipers	Hematoxin	N. Sahara	Buried in sand
	Puff adder	Hematoxin	Arabia, Africa	Open terrain, sluggish
	Gaboon viper	Neurotoxin and hematoxin	Tropical W. Africa	Forests, deadly
	Rhinoceros viper	Hematoxin	Tropical Africa	Wet forests
	Habu viper	Neurotoxin	Okinawa	Caves and dry rocky country
CROTALIDAE front movable hollow	Pit vipers	Predominantly hematoxin	Old and New Worlds, none in Africa	Over 80 species, pit between eye and nostril
Examples	Rattlesnakes*	[illegible]	[illegible]	[illegible]
	Bushmaster	[illegible]	[illegible]	[illegible]
	Fer-de-lance	[illegible]	[illegible] des	[illegible]
	Palm vipers	Hematoxin(?)	S. Mexico, Central and South America	Arboreal, small, greenish. Blue face
	Copperhead	Hematoxin	United States	Dry stony terrain
	Water moccasin	Hematoxin	Southeast U.S.A. to Texas	Swamps
	Asiatic pit vipers	Hematoxin	Southeast Asia, Formosa	Most arboreal

* All rattlesnakes are poisonous.

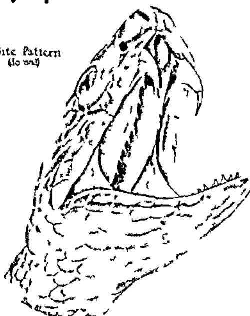


Figure IX.11 Head of a rattlesnake show ng hollow fangs w th sli like opening nea the tip outline of the venom gland teeth in both upper and lower jaws, pit ly ng between but below the level of the eye and nostril, and the vert cal, ellip cal ca like pup l The two fang marks and the teeth marks from the upper jaw are shown in the inset of the dorsal bite pattern (Courtesy of the Louisiana State Univers ty School of Med cine)

the fangs it is necessary to draw or dissect away this covering using appropriate care to avoid direct contact with any of the structures since the severed head of a freshly killed snake may by reflex go through the actions of biting when thus stimulated

Identification The identification of poisonous snakes may be diffi

whatever native advice professional or otherwise may be available The discovery of a pair of fangs in the upper jaw of a specimen is certain *evidence of its poisonous nature If several pairs of enlarged teeth* are present the specimen is probably harmless Other indications but by no means all inclusive are (1) a pit situated between the eye and nostril (2) a vertical slitlike pupil (3) a large triangular head with relatively narrower neck (4) a thick body and stumpy tail (though many poison ous species are whiplike) and (5) a series of unpaired scales immedi ately posterior to the vent

The importance of identifying poisonous snakes lies in the different prognosis and course of treatment indicated for different types of venom Without relation to size various species of snakes deliver characteristic doses of venom that vary both as to quantity and quality Hence the bite of one snake may not be markedly dangerous although a fair quan

tity of venom has been introduced whereas in another case a relatively insignificant bite may be fatal

Venom Various types of venom are produced by snakes These may be divided conveniently into two main classes those that affect the respiratory and other centers in the brain stem or spinal cord (neurotoxins) and those that affect the tissues at the site of injection and possibly also the blood stream in general (hematoxins) The latter components of snake venom include hemolysins cytolysins endotheliolysins and several other lytic coagulant and anticoagulant substances A given species of snake usually has venom that is preponderantly of one type or the other although more or less equal mixtures of the two occur in a few cases

Venom composition is not thoroughly understood Phosphatidases probably play a prominent part in poisoning Lecithinase acts upon lecithin and yields among other factors oleic acid and lysolecithin Lysolecithin like lecithin is hemolytic It also acts on isolated heart muscle causing contractures fibrillation potassium loss and excitability By its action on capillary endothelium it may cause hemorrhage of the lung Phosphatidase action in forming lysolecithin is accompanied by liberation of histamine this may result in a rapid fall of blood pressure Local and later more generalized destruction of capillaries and protein loss intracellularly with resulting loss of vascular osmotic pressure are major causes of the intense swelling and edema following a pit viper bite

The venom of some pit vipers may cause erythrocytic destruction

causing an increase not only in their own invasive powers but in those of bacteria introduced into the wound The cholinesterase activity of elapid venoms is high In contrast the venoms of vipers and pit vipers which are low in neurotoxic action have almost no cholinesterase Possibly the muscular paralysis following elapid bites may be due to the destruction of acetylcholine

It is desirable to know the offending species of snake in evaluating the probable effects of a bite If it is at all possible the victim or his companions should kill the snake and bring it to the place of treatment In a given region the number of dangerous poisonous species is usually small and may be learned quickly In submitting a specimen to a distant laboratory or museum for identification it is not necessary to send the entire reptile—its head in a jar of 70 per cent alcohol or 10 per cent formalin is sufficient

Clinical Characteristics In a case of snake bite when no knowledge of the offending species can be obtained one must examine the wound carefully to appraise its importance Nonpoisonous snakes will often bite man if molested or surprised the only treatment necessary is the prevention of secondary infection The bites of nonpoisonous snakes leave uniform rows of teeth marks or scratches on the skin while the poisonous species show in addition the laterally placed points of

entry of the fangs The latter two marks are distinctly larger, and the distance separating them is some indication as to the size of the snake concerned When only one fang punctures the skin, a proportionately smaller quantity of venom enters and the sequelae may be milder, however, single fang wounds may prove fatal (Fig IX 11, p 632)

If some time has elapsed between the bite and the arrival of the patient at the place of treatment, the victim's condition is a further aid in estimating the potential seriousness of the situation grave symptoms appear rapidly following the efficient injection of highly virulent venom but more slowly in less serious cases However, some neurotoxic venoms are slow to show their effects, especially if the bite is on the lower extremity—the apparently good condition of the patient is *not* a reliable sign in these cases The bitten part shows little local reaction in the case of neurotoxic venoms but is swollen, discolored and painful when infiltrated by the hematoxic type Deaths have occurred as late as two weeks after the bite, although such cases are usually complicated by secondary infection Gas gangrene may become a complication The most fulminating cases are those in which the patient has been bitten on the face

The size of the bitten individual determines how much of the venom will be neutralized by natural processes within the body Children and small adults neutralize less than large persons and are consequently more severely affected by a given quantity of toxin

Since neurotoxic venom produces little local pain, the layman and the inexperienced physician are often misled into treating the bite too casually Delayed systemic reactions may supervene acutely 24 to 48 hours later and lead rapidly to respiratory or cardiac paralysis and death All bites by poisonous snakes should therefore receive prompt attention regardless of the patient's seemingly favorable condition

Treatment. When a person is bitten he should remain quiet if possible, since physical activity accelerates the absorption of venom If the bite is on an arm or leg a tourniquet should be applied proximal to the wound This should not be so tight as to occlude the arterial circulation and should be partially loosened at intervals, not longer than every 20 minutes to prevent complete venous stasis

Immediate The patient should then walk slowly to the nearest [illegible] ate treatment preferably by a physician Snake [illegible] contain iodine [illegible] al suction appli[illegible] [illegible] id that the bite site be incised by criss-cross or parallel incisions Since the fangs are curved and the venom is not released immediately below, but behind the fang marks, the incisions should be made starting at the sites of the wounds and extending backward to a depth and length consistent with the size of the snake and the strength with which it struck Care must be taken to avoid excessively deep incisions Also incisions over thin, bony areas may sever nerves or tendons The metal suction applicator, inserted into the bulb, is applied to each wound in succession venom and serum being sucked out

Others state that suction without incision using the rubber bulb or the mouth alone withdraws the venom efficiently along the preformed tracts of the fangs they believe also that incision increases the area through which venom can be absorbed as well as the surface on which subsequent secondary infection can develop thereby enhancing dangers which may already be considerable

In the light of common practice it would seem that incision and suction should be elected Numerous devices for withdrawing venom may be improvised Ordinary breast pump suction bulbs may be applied to the incisions or heated glass bottles of any size may be used the cooling of their contained air providing a suitable vacuum If oral suction is necessary a square of thin rubber should be placed over the fang marks or surgical incisions to protect the operator's mouth from the venom and to keep the wound as free from bacterial contamination as possible Swallowed venom is inactivated by the digestive juices however significant amounts of it can be absorbed through abrasions or other open lesions of the lips tongue or buccal mucosa

Intermittent suction may profitably be continued for 15 hours at least three quarters of each hour being devoted to evacuation of venom and serum New incisions may be made at the advancing edge of the swelling especially in regions proximal to the bite and suction should be

jet should be moved toward

crystals and whiskey—are now regarded as useless and the latter may even produce fatal results in certain cases

Antivenins Antivenins have been prepared for use in many parts of the world Some of these sera are polyvalent so that in the appropriate geographic region their administration neutralizes whatever toxins are present others are effective only for a particular species the identity of which must therefore be known to the physician If the correct antivenin cannot be obtained however it is always worth using the ones available since most of the individual components of snake venom have at least a partial antigenic relationship and may therefore be neutralized in part by antivenins that are not strictly homologous This is not true however of widely different venoms hematoxins are not inactivated by an antivenin prepared against the neurotoxins of cobras or coral snakes

Antivenin may be injected intravenously or infiltrated about and into the site of the bite subcutaneously and intramuscularly In serious cases the intravenous route is by far the most important Ordinarily intramuscular injection is employed Excessive infiltration of tissues of fingers or toes with antivenin may prove damaging The amount of antivenin to be injected varies with each case Children require more than adults since they neutralize less of the venom with natural substances in their own bodies The progress of the patient will determine how many injections to give apparently there is no contraindication to giving large quantities in serial dosage—the chief requisite is to neutralize whatever venom still remains active

Most antivenins consist of serum from immunized horses An intra

cutaneous test for hypersensitivity should be made prior to their administration and desensitization performed if indicated Immediate incision and suction are of vital importance when hours must be lost in desensitizing the patient Liquid antivenin must be stored in the refrigerator to preserve its potency Modern antivenin manufactured in the United States is now dehydrated and retains its activity at room temperature

Cooling of the extremity at the earliest possible moment is valuable for it reduces the activity and absorption of the venom and lessens pain edema and necrosis The application of ice bags to the area of the bite may be used to supplement the standard measures Controversy exists over the extensive use of cryotherapy in snake venom poisoning instead of incision and suction Certainly extensive damage may result from improper use of cryotherapy The combined use of a tourniquet and cryotherapy and the resultant refrigeration may be dangerous in the presence of venous stasis or in persons with certain vascular disorders The limited use of cooling by application of ice bags or a suitable substitute to the site of the bite and areas of extending edema may be beneficial when employed as an adjunct to tourniquet, incision and suction

Further measures in treatment are chiefly supportive, being designed to combat paralysis or circulatory failure Sedatives are contraindicated as a rule, although some authorities permit the use of morphine for cases with severe pain Donors for transfusion should stand by in case of emergency, repeated blood counts will indicate the need for such treatment

Spitting cobras, of which two species occur in Africa can spray their poison for a distance of eight to 12 feet This venom is often directed at the eyes of the cobra's prey, causing local damage that may result in blindness, it is also absorbed slowly through the conjunctivae and may produce delayed systemic reactions The eyes should be washed out at once with water and then, as soon as possible, with boric acid or Argyrol solution to minimize effects of the venom

Prophylaxis. Prophylaxis against snake bite involves wearing field shoes and leather or heavy canvas puttees in infested areas, since most bites occur on the leg below the knee However, in the absence of such protection loose trouser legs are to be desired in preference to tight fitting riding breeches Most snakes are nocturnal, but they are nevertheless somewhat active while basking in the sun by day

Palm vipers, found in Central and South America, and the water moccasin in the Gulf States of the U S A are especially dangerous to those who attempt to cut trails through thick jungle or underbrush, since the former snakes are arboreal and the latter often climb small trees in order to bask above ground They drop from their perches when disturbed and in doing so many inflict bites on the face As already stated this site permits the most rapid absorption of venom, in addition the venom of these species is highly toxic Arboreal species in other parts of the world constitute a similar menace

Rodent control around camps will remove a source of attraction for snakes In tropical Pacific waters sea snakes may be a danger to bathers

who are tempted to handle these docile and unaggressive creature however they ordinarily have difficulty in inflicting their venomou bites since their small mouths adapt them to a diet of fish

Snakes are not nearly as great a menace as is commonly supposec As a rule they are not aggressive by nature and will try to avoid ma rather than attack him Their relative scarcity in most regions is itsel in assurance against being bitten Many travelers to tropical wilder nesses return months later without having seen a single serpent poisor ous or otherwise

Crocodilians

Among the large reptiles that can injure man mechanically are cro codilians which include the alligators caymans crocodiles and gavial Of these the first three have relatively wide jaws whereas gavials foun only in Africa and the Far East have a long narrow snout All form however possess many sharp teeth in each jaw These animals inhab swamps and slow flowing streams in the tropics and subtropics Ther is only one marine member of the group the salt water crocodile of th Far East and the South Seas It is very common in the Solomons Th others spend much time basking in the sun on the banks of their nativ river or swamp When hungry they enter the water and submerge unt only their eyes and nostrils protrude from the surface An animal swim ming or wading too close is seized and dragged to the bottom Th reptile may then revolve rapidly on its long axis thus twisting o the appendage it has grasped The prey is then seized at another pa and eventually dies as the result of drowning exsanguination and mu tilation

feet in lengtl

Al Employing th

ta grown huma

being Except in certain regions they do not frequently molest ma however being dangerous chiefly in the vicinity of their nests alor river banks or if surprised by a bather who is equally unaware of th reptile s presence Once seized man has only a slim chance of escapin from a large specimen It is said that gouging the reptile s eye with one

further endanger the victim Those who escape usually sustain ragge wounds and great loss of blood

inhabitants Crocodiles are found throughout the tropics caymans and alligators are confined almost exclusively to the Western Hemisphere the exception being a single species of alligator found in China

Bats

Vampire Bats Vampire bats occur in tropical parts of Mexico and Central and South America including Trinidad They are small creatures only three inches long and have front teeth especially modified for cutting skin Their biting is said to be painless They feed exclusively on blood

These bats are greatly feared because of the wealth of legend that surrounds their blood feeding behavior However they are a menace to man only because they have been shown to be capable of transmitting rabies In parts of Mexico it is now known that vampire bats transmit a modified form of rabies virus to cattle causing a disease in these hosts long familiar to the ranchers as derriengue It is suspected although not proved that human beings in the endemic regions also become infected either following bites of vampire bats or after butchering diseased cattle The symptoms in alleged cases may be clinically indistinguishable from poliomyelitis encephalitis or encephalomyelitis and the clinical course does not necessarily lead to death as in canine rabies

Screened quarters or bed nets afford protection against the nocturnal visits of vampire bats Near human habitations or encampments it is often possible to find many of their daytime shelters in caves or hollow trees and destroy them

Insect Eating Bats Within recent years rabid insect eating bats of several species have been noted in widely scattered locations in the United States Human cases of rabies have occurred when curious persons have picked up apparently disabled bats or occasionally after a bat has made an unprovoked attack It is largely a mystery how these bats acquire infection since they do not suck blood However it is known that rabies is endemic among flesh eating mammals in the same environment and a transfer may somehow occur Possibly mosquitoes or some other blood imbibing arthropods play a role either directly by biting or by being eaten by bats after having fed on a rabid animal Moreover it is known that some of the Mexican free tailed bats inhabiting the Carlsbad Caverns occasionally wander far enough south into Mexico to mingle with vampire bats They could thus acquire infection and bring it back on their return to the caverns From here it could spread further through the bat population of the United States during the warm months of the year

Any bats found alive on the ground in daytime should be treated with

great caution If possible they should be pushed into a box or bag with a stick and sent to a laboratory for examination for Negri bodies and animal inoculation Persons already bitten should proceed as in the case of dog bite (see page 41)

A confusing problem in recent years has been the mechanisms by which certain encephalitis viruses normally transmitted by mosquitoes survive over the winter One theory has been that there is a springtime recrudescence of viremia in vertebrate hosts infected during the previous year Others believe that the virus is carried by birds migrating from warmer regions Another theory is that the virus survives in hibernating mosquitoes or in other types of vectors such as mites

These theories fall short of a satisfactory explanation of observed phenomena Recent laboratory work with insect eating bats has shown that bats can become infected with certain of these viruses by the bites of mosquitoes When viremia appears the bats can be refrigerated under conditions that duplicate their normal hibernation At the end of this simulated hibernation period the viremia reappears until normal immunity supervenes Thus wild bats bitten by infected mosquitoes in the fall might serve to infect other mosquitoes in the following year Field investigations should throw light on this possibility as an effective mechanism for the wintering of mosquito borne viruses

X

Medically Important Mollusks

R Tucker Abbott

69

Mollusks and Disease

Introduction

Certain mollusks have become of increasing medical importance because of the direct or indirect injury which they are capable of inflicting or because of their role as intermediate hosts of helminthic parasites of man or animals In the great majority of instances the medically important members of this phylum are restricted to the fresh water snails The exceptions include the fatally venomous cone shells of the Indo-Pacific, certain squids and octopuses which may inflict a poisonous bite, the marine blue mussels that have been a source of *Gonyaulax* food poisoning, the fresh water clams which serve as second intermediate hosts of *Echinostoma*, certain species of terrestrial, pulmonate gastropod snails which serve as intermediate hosts of *Dicrocoelium*, a common parasite of the biliary tract of mammals, and marine snail hosts of dermatitis-producing cercariae

Role of Mollusks as Direct Agents of Human Disease

Five species of the marine cone shells are known to inflict a venomous sting that, in some cases proves fatal to man within four hours Venomous specimens are known only from the coral reefs of the Indian and Pacific oceans The venom is injected through a puncture made in the victim's skin by a half inch long, needle-like, hollow tooth Care should be exercised in handling live specimens over two inches in length The cones are heavy, conic shells with a long, narrow aperture, usually of attractive

coloration and covered with a thin or thick, horny periostracum (Fig X 4)

Octopuses must be large to be dangerous and such specimens are very infrequently encountered in shallow water The secretion from the salivary gland of most octopuses is a proteolytic ferment and the bite of the creature can cause *considerable pain and local swelling*

Blue *mussels* and certain other bivalves found along the open coast especially the West Coast of North America are likely to cause paralytic poisoning if eaten during the summer months A number of human deaths have been reported from this source which is due to the bivalves having ingested certain planktonic organisms (*Gonyaulax*) The toxin is water soluble and is not destroyed by boiling

Role of Mollusks as Carriers of Disease

All species of trematodes parasitic to man have gastropod snails as obligatory intermediate hosts The various species of trematodes have each become adapted to a single, or at most a few species of snails *With other species of snails the miracidia either are not attracted fail to penetrate or else do not complete their larval development* A few snails are capable of experimental infection but are not the natural hosts

The most important human diseases carried by mollusks are listed in Table X 1 and the mollusks are illustrated in Figures X 1 through X 5

Snail Control All trematode parasites of man must pass through a snail intermediate host Interruption of the biologic chain by control of this host constitutes one of the important potential methods of eliminating these trematode diseases of man The application of such control measures however, is neither easy nor always practical Consequently other procedures must be utilized as well Research in the field of snail control by means of molluscicides is still in its infancy and it is doubtful if the optimal agent has yet been developed

In areas where fresh water fish and mollusks are important elements in the local diet, the use of chemical molluscicidal agents may not be permissible because of their lethal effect upon these protein sources and their consequent adverse effects upon the diet and the nutrition of the population Furthermore, such chemical agents must not be toxic for man, domestic animals or plant crops

Snail control operations may be concerned with both the amphibious and aquatic species The semiamphibious prosobranchs (*Oncomelania* and *Pomatiopsis*) are controlled best by spraying their habitat with sodium pentachlorophenate (Santobrite) or dinitro o cyclohexylphenol (DCHP) at a rate of about 20 to 30 lb per acre (lethal to snails at 1 to 2 ppm) Treatment should be repeated *at least* twice a year, if eggs and surviving adult stragglers are to be eliminated

The fresh water pulmonates (*Lymnaea Australorbis, Planorbis* and others), aquatic snails are best attacked by the use of copper sulfate (lethal to snails at 10 ppm) sodium pentachlorophenate (Santobrite) 5 to 15 ppm or other molluscicidal agents These may be applied in the form of an aqueous spray *by dusting or by immersion* of bags or porous balls containing the chemical

Schistosomiasis japonica	*Schistosoma japonicum*	*Oncomelania quadrasi* *Oncomelania formosana* *Oncomelania nosophora* *Oncomelania hupensis* *Pomatiopsis lapidaria*	Philippine Islands Formosa Japan and China China U S A (experimental)	Hydrobiidae	None
Schistosomiasis haematobia	*Schistosoma haematobium*	*Bulinus truncatus* *Bulinus africanus* *Bulinus forskali*	North half of Africa South half of Africa Mauritius	Bulinidae	None
Schistosomiasis mansoni	*Schistosoma mansoni*	*Biomphalaria alexandrina* *Biomphalaria pfeifferi* *Australorbis glabratus* *Tropicorbis havanensis*	Northern Africa Southern Africa South America West Indies U S A (experimental)	Planorbidae	None
Clonorchiasis	*Clonorchis sinensis*	*Hua ningpoensis* *Bulimus fuchsianus* *Alocinma longicornis* *Parafossarulus manchouricus*	China China China and India China and Japan	Thiaridae Hydrobiidae Hydrobiidae Hydrobiidae	Fresh-water cypri noid fishes
Opisthorchiasis	*Opisthorchis felineus*	*Bulimus tentaculatus*	Northern Europe, N E United States	Hydrobiidae	Cyprinoid fishes
Fascioliasis	*Fasciola hepatica*	Several species of *Lymnaea* *Succinea* sp *Praticolella* sp *Pomacea*	Worldwide Worldwide Europe Worldwide	Lymnaeidae Succineidae Polygyridae Viviparidae	Encysts on grass and herbs
Fasciolopsiasis	*Fasciolopsis buski*	*Segmentina hemisphaerula* *Hippeutis cantori* *Gyraulus saigonensis*	Eastern Asia Eastern Asia	Planorbidae	Encysts on water plants
Paragonimiasis	*Paragonimus westermani*	*Semisulcospira libertina* *Semisulcospira amurensis* *Thiara granifera* *Hua toucheana*	North China, Japan North China, Korea Formosa to Hawaii	Thiaridae	Fresh water crabs and crayfish
Metagonimiasis	*Metagonimus yokogawai*	*Semisulcospira libertina* *Thiara granifera*	North China, Japan S E Asia to Hawaii	Thiaridae	Salmonoid, cypri-noid fishes

Limited field trials in Japan, Nigeria, the Dominican Republic and South America indicate that effective snail control may be obtained at reasonable cost using sodium pentachlorophenate (Santobrite), or DN 1 (40 per cent dinitro *o* cyclohexylphenol) The results reported must be regarded as preliminary until more extensive evaluations have been made

In some areas successful control operations may require combining chemical treatment with drainage and alteration of the local environment of the snail species under attack

70

Structure, Classification and Biology of Medically Important Mollusks

Field surveys and control operations directed against snails of medical importance require accurate identification of the various species of mollusks which may be encountered This is frequently difficult Although several important species of molluscan intermediate hosts are easily identified, there are many medically unimportant species possessing shells which superficially resemble those of species which carry pathogenic parasites A further difficulty lies in the fact that there are many major families the systematics and nomenclature of which are still in a state of flux

... ani

... iape

... the

2 Pelecypoda (Lamellibranchia) clams, mussels, oys...

... shells

... secretes a calcare-ous shell The buccal mass, except in the Pelecypoda, contains a radular ribbon of hard denticulate teeth

Mollusks are either bisexual, hermaphroditic or capable of changing

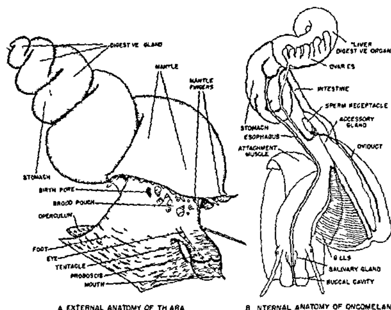


Figure X.1 Gross anatomy of the prosobranch snail. (A) *Thiara granifera* (left) is the oriental host of *Paragonimus* and (B) *Oncomelania quadrasi* (right) is the Philippine host of *Schistosoma japonicum* (Redrawn from Abbott.)

sex one or more times during their life span The eggs may be shed freely into the water laid in capsules or brooded within the parent

Class Gastropoda

Subclass Prosobranchia

The subclass Prosobranchia (Streptoneura) are the operculate snails which possess a horny or calcareous *operculum* that is usually attached
nerve loop is crossed,
ttached to the inside
are hermaphroditic,
subclass is generally
divided into three orders

1 Archaeogastropoda (Scutibranchiata) a group of primitive, mainly marine snails of no medical importance

lass contains the
They are charac-

entire length

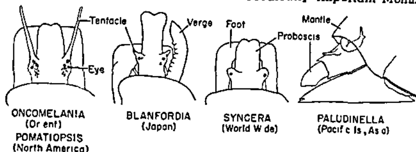


Figure X.2 Anatomy of small brown Hydrobid snails with a horny operculum. *Oncomelania* and *Pomatiopsis* are hosts of oriental schistosomiasis the other genera are not carriers (Redrawn from Abbott.)

3 Neogastropoda marine snails, including the venomous cone shells They are characterized by one to three transverse rows of strong radular teeth

Order Mesogastropoda. *Family Hydrobudae* The family HYDROBIIDAE (AMNICOLIDAE, BITHYNIIDAE) comprises two subfamilies, the HYDROBIINAE (Fig X 2) and the BULIMINAE These are of considerable medical importance, since the former contains the only known intermediate hosts of *Schistosoma japonicum* and the latter the majority of the first intermediate hosts of the biliary flukes, *Clonorchis* and *Opisthorchis*

The members of this family are small, aquatic or amphibious gastropods with slender or subspherical shells which rarely exceed a length of 10 mm The sexes are separate The males possess an external copulatory organ, known as the *verge*, attached to the right side of the body and appearing as a single or multipronged finger The mantle edge is smooth The operculum is either horny or calcareous Eggs are laid in gelatinous packets and may be covered with mud or tiny pebbles

Subfamily Hydrobunae Members of the subfamily HYDROBIINAE are characterized by (1) thin, horny and paucispiral opercula, (2) males having a fleshy verge which may be frilled along its edge

varix or thickening of the rim Three of the species have smooth, brownish slender shells, the fourth, *O hupensis*, has ten to 30 small, axial ribs per whorl and is yellowish brown in color The verge is a simple prong The most characteristic feature is a streak of small, yellowish granules over each eye, forming a false "eyebrow" The four species are

1 *Oncomelania hupensis* Gredler

SYNONYMS *Oncomelania schmackeri* Moellendorff, *longiscata* Heude, *elongata* Bartsch, *yaoi* Bartsch, *multicosta* Bartsch and *anhuinensis* Li

DISTRIBUTION This species is common in the canals in the Yangtze River basin in the provinces of Kiangsu Chekiang Anhwei, Kiangsi and Hupeh It is the principal host of *Schistosoma japonicum* in China (Fig X 4)

The adults are gray brown to waxy yellow in color They are 7 to 10

mm in length and have six to nine whorls Each whorl has ten to 30 small axial ribs, and nuclear whorls may be tinged with rose

2 *Oncomelania nosophora* Robson

DISTRIBUTION It is common in or along small creeks, irrigation ditches, rice paddies or unflooded river bottoms in China, south of the Yangtze, and on Honshu and Kyushu Islands, Japan It is the only known host of *S japonicum* in Japan

The adults are dark to light chestnut brown They measure 5 to 12 mm in length, are smooth, and have six to nine whorls

3 *Oncomelania formosana* Pilsbry and Hirase

DISTRIBUTION This species is common in rice paddies and irrigation ditches in the western half of Formosa It is the only host of *S japonicum* in Formosa

The adults are light chestnut brown in color, relatively smooth and 4 to 6 mm long The length of the last whorl is always greater than that of the whorls above

4 *Oncomelania quadrasi* Moellendorff

SYNONYM *O hydrobiopsis* Rensch

DISTRIBUTION This species is common in small creeks and among the vegetation above the waterline of slow flowing streams in eastern Leyte, eastern Mindoro, Mindanao, Samar and Sorsogon Province, Luzon Island Philippines It is the only known intermediate host of *S japonicum* in these islands

The adults are translucent chocolate-brown sometimes covered with a thin, black, encrusting slime, relatively smooth and 3 to 5 mm in length The last whorl is always longer than those in the spine *Oncomelania quadrasi* resembles and may be confused with *Syncera*

Genus Blanfordia Members of this genus are restricted to the Japanese Islands Despite their close resemblance to *Oncomelania*, they have never been implicated as carriers of schistosomiasis There are four species, of which *B simplex* Pilsbry from Honshu is the commonest The shells are not as slender as those of *Oncomelania* species The verge is a simple prong with strong serrations on the inner concave edge There [illegible] peduncles are well [illegible] projecting forward

Genus Pomatiopsis This is an American genus with shells and bodies that closely resemble those of *Oncomelania*

DISTRIBUTION This genus is found in woodland swamps and on low river banks in the United States from Minnesota east to New York, south to Alabama and Texas, and on the Atlantic seaboard from Pennsylvania south to Virginia

[illegible]

soma japonicum

The shell is brownish, 5 to 8 mm in length, and resembles that of *Oncomelania nosophora* The verge is a flat, meat cleaver-shaped prong

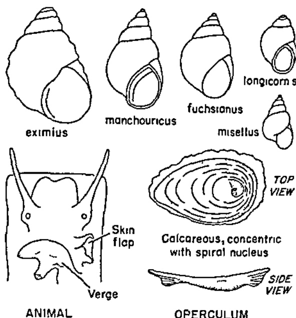


Figure X 3 The Bulimoid snails of the Orient serve as the main hosts of *Clonorchis* and *Opisthorchis* (Redrawn from Abbott)

with a variable number of serrations on the inner, concave edge There are yellow color granules above the eyes

Genus Fukuia Two species are known in this Japanese genus which is not of medical importance The shells resemble those of *Oncomelania* but are more ovate much thicker glossy, reddish brown and without a thickened outer lip The spiral sculpturing consists of numerous microscopic, incised lines

The verge is a single prong bearing a rather large button like gland on the upper side The tentacles are very short Yellow granules are present behind the eyes

Subfamily Buliminae The subfamily BULIMINAE contains the majority of the first intermediate hosts of the human biliary flukes *Clonorchis* and *Opisthorchis* (Fig X3) The following genera sometimes treated as subgenera of the genus *Bulimus* (formerly *Bithynia*) are all of medical importance

1 *Bulimus* (north temperate regions)
2 *Alocinma* (India and China),
3 *Parafossarulus* (eastern Asia)

Members of this subfamily are characterized by (1) a thick calcareous operculum (2) a verge with a lateral finger like appendage (3) a small cup shaped skin flap attached to the right side of the head just behind the right tentacle The genera are distinguished by shell characteristics

Genus Bulimus 1 *Bulimus fuchsianus* Moellendorff

DISTRIBUTION This genus is especially common in southern China where it serves as the principal snail host of *Clonorchis sinensis* (Fig X3)

The adult shell is greenish brown and about 10 mm long It is rather fragile and smooth, with a dull finish and fragile outer lip The whorls are well rounded

The mantle is black with numerous small, round spots of translucent cream, and the animal is gray with many brilliant orange red spots

2 *Bulimus misellus* Gredler This is a common, medically unimportant Asiatic species (Fig X 3).

The adult shell is 5 to 7 mm in length with five well rounded whorls It is distinguished from *B fuchsianus* by its smaller, more slender shell and its mantle, which is cream colored with sparse, black, cobwebby mottlings

3 *Bulimus tentaculatus* Linn

DISTRIBUTION This is a common north European species in lakes and ponds which has become established in the north central and north eastern United States It is one of the principal snail hosts of the liver fluke, *Opisthorchis felineus*

The shell is yellowish, greenish or brownish and 5 to 11 mm long The operculum is calcareous The animal is yellowish white with a blackish head and proboscis, and with a few golden yellow spots The outer marginal radular tooth has approximately 16 denticles the inner marginal approximately 12 the central, seven at the top edge and approximately six at each lower corner

Genus Alocinma 1 *Alocinma longicornis* Benson

DISTRIBUTION This snail is common in canals and ponds in China, where it serves as one of the intermediate hosts of *Clonorchis sinensis* (Fig X 3)

The adult shell is 5 to 8 mm in length, smooth and globular with a short [illegible]
color
have
white blotches

Genus Parafossarulus 1 *Parafossarulus manchouricus* Bourguignat

SYNONYM *Bithynia striatula* Benson

DISTRIBUTION This species is common in ponds in China, Formosa Korea and Japan (Fig X 3) It is the principal intermediate host of *Clonorchis sinensis* in Japan and the second most important in China It likewise carries *Opisthorchis felineus* and *Echinochasmus perfoliatus*

The adult shell is yellowish to greenish brown and 7 to 10 mm long [illegible]

and the top visceral whorls are pinkish tan The tentacles have an internal black core

2 *Parafossarulus eximius* Frauenfeld This largest of all Chinese bulimoid snails is common in lakes and ponds in eastern and central China It is not of medical importance (Fig X 3)

The shell is reddish brown in color, reaching a length of 17 mm There are three to four strong spiral cords on each whorl

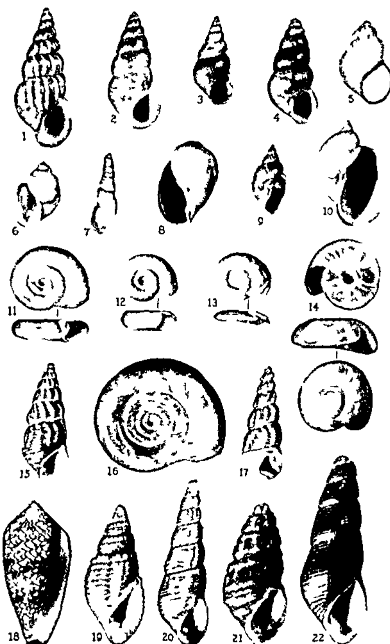


Figure X 4 Medically important mollusks 1 *Oncomelan a hupens s* Gredler (China) 2 *O nosophora* Robson (China and Japan) 3 *O quadrası* Mlldff (Philippines) 4 *Pomatiops s lap dar a* Say (United States and Canada) (1–4 all 4 ×) 5 *Bulimus tentaculatus* L. (United States northern Europe) (3 ×) 6 *Bul nus truncatus* Audouin (Africa and Asia Minor) 7 *Bulinus forskali* Ehrenberg (Mauritius Africa) 8 *Bul nus (Physops s) africanus* Krauss (Africa) 9 *Lymnaea ollula* Gould (Hawaii and China) 10 *Lymnaea aur cularia* L. (northern Eurasia) 11 *B omphalar a alexandrina* Ehrenberg (north

Family Assimineidae (Syncendae) This is a large family of small snails found mainly in tropical and subtropical areas, some members of which closely resemble schistosomiasis carriers such as *Oncomelania* The group is of little medical importance, although *Assiminea lutea* Adams is reported to be a minor host of *Paragonimus westermani* in southern China These snails are amphibious or terrestrial with shells less than 8 mm in length and with a translucent horny, paucispiral operculum The animals of *Assiminea* (formerly *Syncera*) have very short stubby tentacles welded to the eyestalk, and the shell has a single, microscopic, spiral thread just below the suture of the whorls A similar, terrestrial genus, *Paludinella*, lacks this thread and its animal has short tentacles and a short cape encircling the upper part of the proboscis

Family Thiaridae (Melaniidae) The THIARIDAE is a widely distributed and diversified family of operculate snails living in fresh and brackish water A number of species are the main snail hosts for *Paragonimus*, *Metagonimus*, *Troglotrema* (salmon poisoning), *Haplorchis* and *Diorchitrema* The shells are usually 1 to 3 inches in length, black or brown and fairly slender There are two major subfamilies the true THIARINAE, in which the young are brooded in a neck pouch and in which the mantle edge is digitate, and the PLEUROCERINAE, whose members lay eggs or brood the young in a uterine pouch and whose mantle edge is smooth or wavy but never digitate This family has been generally referred to as MELANIIDAE in medical literature

Subfamily Thiarinae *Thiara (Tarebia) granifera* Lamarck This common species lives in fast flowing streams in southeast Asia, Indonesia, Formosa and the western Pacific islands, where it serves as the first intermediate host for *Paragonimus westermani*, *Metagonimus yokogawai*, *Diorchitrema formosanum* and *Haplorchis taichui* (Fig X 4) The snail has also become established in Lithia Spring Florida Adults are 6 to 40 mm long elongate turrite yellowish to reddish brown have whorls with four to six spiral rows of round to quadrate small beads and a fragile outer lip The mantle edge has several prominent fleshy digitations four of which may be seen projecting beyond the shell lip on the left side Mature specimens have shelled young in a brood pouch under the skin behind the head The operculum is two-thirds the size of the aperture,

[illegible]

The animal is similar to that of the above species (Fig X 4) The shell is 1 to 2 inches long and slender, with well rounded whorls and sculp-

---

ern Africa) 12 *Biomphalaria pfeifferi* Krauss (southern Africa) 13 *Hippeutis cantori* Benson (China) 14 *Segmentina hemisphaerula* Benson (eastern Asia) (5 ×) 15 *Goniobasis silicula* Gould (northwest United States) 16 *Australorbis glabratus* Say (West Indies and South America) 17 *Hua ningpoensis* Lea (China) 18 *Conus textile* L. (Indo-Pacific reefs) 19 *Thiara (Tarebia) granifera* Lamarck (southeast Asia Pacific Ids) 20 *Thiara (Melanoides) tuberculata* Muller (Africa to S E Asia Pacific Islands) 21 *Semisulcospira amurensis* Gerstfeldt (northern China Korea) 22 *Semisulcospira libertina* Gould (Japan to Formosa) (Numbers 6 to 22 are 1½ × except 14)

turing of numerous axial and spiral threads It is brownish and sometimes mottled with reddish brown This species is a host for *Diorchitrema formosanum* and is suspected to be a minor host for *Clonorchis sinensis*

Subfamily Pleurocerinae *Semisulcospira libertina* Gould This species is considered to be the main intermediate snail host of *Paragonimus westermani* in the Orient (Fig X 4) It has an insular distribution which extends from Japan and Korea to Formosa The shell is ¾ to 2 inches in length somewhat spindle shaped and has slightly flattened fairly smooth whorls Length of the aperture is about half the total length of the shell The whorls have numerous fine spiral threads It is brownish to yellowish brown but sometimes heavily flushed with greenish blue The edge of the mantle is smooth and the uterus on the inside of the mantle may be filled with many, equal sized small young The males lack a verge

Semisulcospira amurensis Gerstfeldt is common in fast flowing streams in northern China and Korea (Fig X 4) It is an intermediate host of *Paragonimus westermani* This species has many minor races in Korea The shell is ½ to 1 inch in length dark brown to greenish brown and usually heavily sculptured with two or three very strong cords on the base of the shell Blunt axial ribs and low nodules are sometimes present The animal is similar to the above species the operculum is opaque brown horny and paucispiral

Hua (Namrutua) ningpoensis Lea is very common in canals and small rivers of central and southern China where it serves as one of the main intermediate hosts of *Clonorchis sinensis* (Fig X 4) It was formerly known as *Melania cancellata* Benson The operculum is translucent thin horny and paucispiral The shell is about 1 inch in length and slender the upper two thirds of each whorl have even strong slightly curved axial ribs and there are three or four smooth spiral cords on the base of the shell The animal lays eggs The mantle edge is wavy but without digitations

Goniobasis silicula Gould This is the only known snail host of *Troglotrema salmincola* Chapin the trematode associated with "salmon poisoning" in northwestern United States (Fig X 4) It is common in lakes and creeks of Washington and Oregon The shell is ½ to 1 inch long brownish to greenish slender and has rounded whorls Strong axial ribs are usually present on the first few whorls and the numerous spiral threads are strongest on the last whorl It is erroneously listed in the literature as *Galbaplicifera silicula*

Family Potamididae These are slender operculated snails found on mud flats in brackish water areas The genera *Pirenella* and *Cerithidea* are known to serve as the first intermediate hosts of *Heterophyes heterophyes* in Egypt and Japan

Families Viviparidae and Pilidae These are the large apple snails [illegible]

centric nucleus near the margin Females brood [illegible] uterus In the males the right tentacle is truncate or recurved and serves as the penis The eyes are on large bulbous swellings at the base of the tentacles The central tooth of the radula is quadrate and denticulate

only on the top edge In the PILIDAE, which have similarly large, 3 inch shells, the operculum is calcareous, the tentacles are very long and slender and the penis arises from the right side of the mantle edge The females lay clusters of pea sized calcareous eggs on reeds just above the surface of the water The genera *Pila* and *Pomacea* belong in this last family but are of little medical importance

Subclass Euthyneura

Order Pulmonata. *Suborder Basommatophora.* *Family Planorbidae* The planorbid pond snails are worldwide in distribution and play an important part in the life cycle of many trematodes The foot of the planorbs is elongate, truncate in front and usually tapers to a point behind Above and in front of the foot is a short, broad, fleshy velum which bears the head and two tentacles The small, black eyes are situated at the inner bases of the tentacles The respiratory opening and pseudobranch or false gill are on the left side of the body The genital openings are also on the left side There is no operculum The animals are monoecious and lay gelatinous globs in which the eggs are embedded (Fig X.5)

Australorbis glabratus Say This species and its several minor races are the main intermediate hosts of *Schistosoma mansoni* in the West Indies and South America (Figs X 4, X 5) It is the largest species in those areas and reaches a diameter of a little over an inch The shell is smooth and made up of slowly widening whorls which are either rounded or slightly angular in cross section The color of the animal is gray or black, and the mantle is mottled with brown or cinnamon Difficulties arise in separating small specimens from several innocent species, but by comparing a graded growth series it is possible to distinguish *Australorbis* from *Drepanotrema* (which has a V-shaped black mark on the velum be

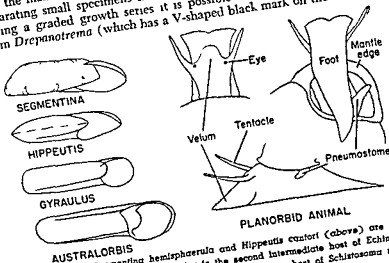


Figure X.5. *Segmentina hemisphaerula* and *Hippeutis cantori* (above) are … hosts of *Fasciolopsis buski* *Gyraulus* is the second intermediate host of *Echin*… *Australorbis glabratus* (above) is the tropical American host of *Schistosoma m*… (Redrawn from Abbott.)

tween the tentacles) and *Tropicorbis* by observing the color patterns of the animal and the shape of the shell Among the synonyms or races of this species are *Planorbis guadaloupensis*, *P olivaceus* and *P antigcunsis*

Biomphalaria alexandrina Ehrenberg This is the main snail host of *Schistosoma mansoni* found in the northern third of Africa It is variable in shape and has been called *Planorbis boissyi* Potiez and Michaud and *Planorbis ruppelli* Dunker The shells are typically planorbid An adult specimen from Egypt has five whorls a diameter of 17 mm and a height of 5 5 mm The upper side of the shell is slightly concave but almost flat and the apex is not very deep The upper part of the aperture is usually arched and may be a little higher than the next to the last whorl The aperture is more or less evenly oval in cross section

Biomphalaria pfeifferi Krauss This is the main host of *S mansoni* in central and southern Africa It is considered a subspecies of the above species by some workers It is similar to *B alexandrina*, but is generally not as flat (diameter 12 mm, height 4 2 mm) and is much more concave at the top with a deep apex The upper part of the aperture is generally less arched, and the aperture has a tendency to be more pinched or triangular in cross section In both species the young shells may have small whitish teeth or folds within the aperture The systematic and nomenclatural *classification of the genus is still unsatisfactory*

Segmentina hemisphaerula Benson In eastern Asia this small common species serves as one of the intermediate hosts of *Fasciolopsis buski* (Figs X 4 X 5) The adult shell is "fat" with a height of about 3 mm and a diameter of 7 to 9 mm It is glossy reddish brown to light brown and the umbilicus is very deep The internal calcareous lamellae are visible through the shell *Planorbis nitidellus* von Martens is a synonym

Hippeutis cantori Benson In eastern China this species is one of the main intermediate hosts of *Fasciolopsis buski* (Figs X 4 X 5) The adults are fairly large (8 to 10 mm in diameter) but rather flat (1 to 2 mm in height) The spire is slightly concave, the umbilicus very wide but not very deep *The periphery of the last embracing whorl may* be sharp there are no internal shell folds It is a glossy translucent brown and is common in ponds and lakes A similar species *H umbilicalis* Benson is fatter (6 by 2 mm), with a neatly indented spire and a much narrower umbilicus It is of no known medical importance

In addition, species of *Helisoma Gyraulus Polypylis* (Planorbidae) and Lymnaeidae serve as fresh water intermediate hosts of various non human schistosomes whose cercariae may produce a dermatitis in man Also, certain marine snails including *Nassarius obsoletus* (= *Nassa obsoleta*), *Littorina planaxis* and *Haminoea antillarum guadalupensis* have ... cause a der

... nus are the

... ntermediate hosts of *Schistosoma haematobium* in Africa Some

Bulinus (*Bulinus*) *truncatus* Audouin This is a widespread species and in most parts of Africa and in Asia Minor It appears to be the ...ain host of *S haematobium* in the northern third of Africa (Fig X4) ...robable synonyms of this species are *Bulinus contortus* Michaud *B* ...*rocchi* Ehrenberg and *B tropicus* Krauss The adults are about 8 to ...3 mm in length sinistral brownish and not very glossy Microscopic ...xial growth lines are irregular The columbella is thin and is not rolled back to form a ridge callus or tube and not abruptly truncate at the base Three to four whorls are present

2 *Bulinus* (*Physopsis*) *africanus* Krauss This is the main carrier of *S haematobium* in South East West and Central Africa (Fig X4) It has several races or ecologic types which have been named *globosa* Morelet *nasuta* von Martens and *ovoidea* Bourg It is similar to *B truncatus* but may reach a length of 19 mm It is usually quite glossy and has a reflected columella which is strongly twisted and truncate below There is microscopic sculpturing of growth lines and very fine punctate dots or short crowded wavy threads The spire may be high or low It is common

3 *Bulinus* (*Pyrgophysa*) *forskali* Ehrenberg This species has been shown to carry *S haematobium* in Mauritius but the range extends over the southern half of Africa (Fig X4) The adult shell is about 13 mm in length elongate with a high spire whose five to six whorls usually have flattish sides Its color is buff to whitish This is a moderately common species

Family Lymnaeidae The genus *Lymnaea* a group of dextrally coiled pond snails is of moderate importance and some of its species such as *L auricularia* Linné *L ollula* Gould and *L bulimoides* Lea serve as the first intermediate hosts of *Fasciola hepatica* "Swimmer's itch" or schistosome dermatitis is caused by nonhuman schistosomes and in many areas of the United States the snail hosts are species of *Lymnaea* Identification of the lymneid mollusks generally requires the services of an expert The head tentacles and eyes resemble those of the planorbs but the genital openings are on the right side of the body There is no operculum (Fig X4)

Suborder Stylommatophora The slugs and garden snails are characterized by their two pairs of head tentacles with the eyes at the tips of the second pair There are many thousands of species of land snails but only relatively few have been found to serve as snail hosts to trematodes infecting man The following families and genera have been shown to carry *Dicrocoelium dendriticum* PUPILLIDAE (*Chondrina*) (=*Torquilla*) FRUTICICOLIDAE (*Bradybaena*) HELICIDAE (*Helicella* *Cochlicella* and *Zebrina*) CIONELLIDAE (*Cionella*) The sheep liver fluke *Fasciola hepatica* is carried by *Lymnaea* and the following land groups SUCCINEIDAE (*Succinea*) and POLYGYRIDAE (*Praticolella*)

XI

Medically Important Arthropods

71

Introduction

Revised by Carroll N Smith

In the foregoing chapters it has been made apparent that many of the important tropical diseases depend for their dissemination upon various species of insects ticks mites and other arthropods whose behavior and life cycles are intimately involved with the continued existence of the parasites concerned In addition to their role as *vectors* of disease the arthropods also include a number of species which hold an important place in medical science by reason of their ability to function *directly* as agents of human disease or discomfort, that is to serve themselves as eti ologic agents of various pathologic conditions Before proceeding to a discussion of particular groups it will be desirable to consider each of these aspects

Role of Arthropods as Vectors of Disease

Table XI 1 presents a recapitulation of all important parasitic diseases in which arthropod vectors are concerned Column 4 shows that at least

Table XI 1. Human Diseases Transmitted by Arthropods

HELMINTHIC DISEASES

DISEASE	ETIOLOGIC AGENT	GEOGRAPHIC DISTRIBUTION	VECTOR	RESERVOIR	LOCATION OF ETIOLOGIC AGENT IN MAN	DIAGNOSTIC PROCEDURES
Loiasis	*Loa loa*	Tropical Africa, especially Congo River basin	Mango flies (*Chrysops dimidiata* and *C. silacea*)	Man	Subcutaneous tissues microfilariae in blood	Clinical picture worm beneath skin blood *exam., day*
Filariasis	*Wuchereria bancrofti* and *W. malayi*	Tropical Africa, Asia Australia South America Pacific Islands	Mosquitoes (*Culex Aedes Anopheles* and *Mansonia* spp.)	Man	Lymph nodes and vessels microfilariae in blood	Clinical picture worms in lymph nodes microfilariae in blood or chyle
Onchocerciasis	*Onchocerca volvulus*	Africa Mexico Central America Venezuela	Blackflies (*Simulium* spp.)	Man	Nodules and tumors microfilariae in skin eyes	Puncture of tumors and nodules biopsy skin section
(1) Ozzard's filariasis (2) Acanthocheilonemiasis	(1) *Mansonella ozzardi* & (2) *Acanthocheilonema perstans*	(1) Latin America (2) Latin America and Africa	Midges (*Culicoides* spp.)	Man	Microfilariae in peripheral blood rarely pathogenic	Blood smear
Dracunculiasis	*Dracunculus medinensis*	Africa India U S S R Middle East	*Cyclops* spp	Man	Loose connective tissue	Roentgenograms
Diphyllobothriasis	*Diphyllobothrium latum*	Northern Europe northern U S A U S S R	Copepods (*Diaptomus* and *Cyclops*)	Man dog cat fox bear etc	Intestine	Fecal examination
Sparganosis	Spargana of several species of tapeworms	Asia scattered areas including Holland British Guiana and U S A	*Cyclops* spp	Man* frogs, snakes, birds mammals	Subcutaneous tissues	Excision (?)
Dipylidiasis	*Dipylidium caninum*	Europe Asia U S A Africa, Pacific Islands	Fleas dog louse (?)	Man dog	Intestine	Fecal examination
Hymenolepiasis diminuta	*Hymenolepis diminuta*	India U S S R Japan Italy U S A	Fleas cockroaches meal worms	Man rat mouse	Intestine	Fecal examination
Hymenolepiasis nana	*Hymenolepis nana*	Cosmopolitan	Fleas (?) mealworms (?)	Man mouse	Intestine	Fecal examination
Paragonimiasis	*Paragonimus westermani* *P. ohirai*	Far East	Fresh water crabs and crayfish	Man carnivores	Lungs, intestinal mucosa	Examination of sputum and feces

* Maturity not reached in man

			PROTOZOAL DISEASES			
Malaria	*Plasmodium vivax*, *P. malariae*, *P. falciparum*, *P. ovale*	Worldwide (see exceptions in certain Pacific Islands, Arctic, Antarctic)	Mosquitoes (*Anopheles* spp.)	Man	Erythrocytes, hepatic parenchyma	Blood smear
African sleeping sickness	*Trypanosoma gambiense*, *T. rhodesiense*	Africa	Tsetse flies (*Glossina* spp.)	Man, game (?)	Peripheral blood, spinal fluid, lymph nodes	Stained blood smear or fresh preparation, lumbar puncture, lymph node puncture
Chagas' disease (South American trypanosomiasis)	*Trypanosoma cruzi*	South America, Central America, Mexico	Kissing bugs (*Triatoma*, *Panstrongylus* spp.)	Armadillo, opossum, dogs, cats, rodents, etc.	Peripheral blood, heart muscle, etc.	Blood smear and culture (N.N.N.), complement fixation, animal inoculation, xenodiagnosis
Kala-azar (visceral leishmaniasis)	*Leishmania donovani*	China, India, Mediterranean, South America	Sandflies (*Phlebotomus* spp.)	Man, dogs	Spleen, liver, bone marrow, reticuloendothelial system	Sternal marrow biopsy, spleen puncture, blood culture (N.N.N.)
Oriental sore (cutaneous leishmaniasis)	*Leishmania tropica*	Mediterranean, Asia Minor, India, China	Sandflies (*Phlebotomus* spp.)	Man	Skin lesions	Smear and culture of lesions (N.N.N.)
South American cutaneous and mucocutaneous leishmaniasis (uta, espundia)	*Leishmania braziliensis*	Latin America	Sandflies (*Phlebotomus* spp.)	Man	Skin and mucous membrane lesions	Smear and culture of lesions (N.N.N.), Montenegro intradermal test
			SPIROCHETAL DISEASES			
Relapsing fever, louse-borne	*Borrelia recurrentis* [?]	Europe, Asia, Africa [?]	Human body louse (*Pediculus humanus humanus*) [?]	Man	Peripheral blood	Direct and darkfield exam and animal inoculation of blood
Relapsing fever, tick-borne	*Borrelia duttoni* [?]	Africa, America, Europe, Asia	Soft ticks (*Ornithodoros* spp.)	Ticks, rodents and other mammals	Peripheral blood	Direct and darkfield exam and animal inoculation of blood
Yaws	*Treponema pertenue*	Tropics	Eye gnat (*Hippelates* sp.)	Man	Skin lesions	Clinical picture, Kahn test
			BACTERIAL DISEASES			
Bubonic plague	*Pasteurella pestis*	Cosmopolitan	Rat fleas, especially *Xenopsylla cheopis*	Rats and wild rodents	Blood stream, lymph nodes	Lymph node puncture, blood culture
Tularemia	*Pasteurella tularensis*	United States, Canada, Japan, Europe, Turkey	Hard ticks (*Dermacentor andersoni* and *D. variabilis*), deer fly (*Chrysops discalis*)	Rabbit and other wild animals	Blood stream, lymph nodes, skin lesions	Clinical picture, agglutination, animal inoculation

Table XI 1. Human Diseases Transmitted by Arthropods—Bacterial Diseases (Continued)

DISEASE	ETIOLOGIC AGENT	GEOGRAPHIC DISTRIBUTION	VECTOR	RESERVOIR	LOCATION OF ETIOLOGIC AGENT IN MAN	DIAGNOSTIC PROCEDURES
Verruga peruana (Oroya fever, bartonellosis)	*Bartonella bacilliformis*	Peru, Colombia, Ecuador, altitude 1 00–10,000 ft	Sandflies (*Phlebotomus* spp.)	Man	Erythrocytes, reticulo-endothelial system	Clinical picture, blood smear and culture, perhaps biopsy of skin lesion
Catarrhal conjunctivitis	Koch Weeks bacillus (?)	Tropical and temperate regions, especially Egypt	Eye gnats (*Hippelates*, *Siphunculina* spp.) mechanical transmission	Man	Conjunctiva	Clinical picture, smear of exudate
RICKETTSIAL DISEASES						
Epidemic typhus, Brill's disease	*Rickettsia prowazeki*	All Continents except Australia	Human body louse (*Pediculus humanus humanus*)	Man	Intracellular (intracytoplasmic)	Clinical picture, Weil-Felix test, specific complement fixation and agglutination
Murine typhus	*Rickettsia typhi*	All Continents	Rat fleas, especially *Xenopsylla cheopis*, also *X. astia* and *Nosopsyllus fasciatus*	Rats	Intracellular (intracytoplasmic)	
American spotted fever	*Rickettsia rickettsii*	Canada, United States, Mexico, Panama, Colombia, Brazil	Ticks: *Dermacentor andersoni*, *D. variabilis*, *Amblyomma americanum*. In Mexico *Rhipicephalus sanguineus* and *A. cajennense*. In South America *A. cajennense* principally	Rodents (?), ticks	Intracellular (intranuclear)	Clinical picture, Weil-Felix test, complement fixation
Fièvre boutonneuse (including Kenya typhus, South African tick bite fever and Indian tick typhus)	*Rickettsia conorii*	Mediterranean, Crimea, Africa, India	Ticks: *Rhipicephalus sanguineus*, *R. evertsi*, *Amblyomma hebraeum*, *Haemaphysalis leachi* and probably others, in appropriate geographic areas	Ticks, dogs (?), wild animals (?)	Initial lesion and lymphatics. Endothelial cells	Clinical picture, Weil-Felix test
North Queensland tick typhus	*Rickettsia australis*	Queensland	*Ixodes holocyclus* (?)	Unknown	Intracellular (intranuclear)	Clinical picture, Weil-Felix test, complement fixation

Siberian tick typhus	*Rickettsia* sp	Central and Eastern Siberia	Ticks *Dermacentor silvarum D nuttali Haemaphysalis concinna*	Ticks, rodents (?)	Blood (and probably tissues)	Clinical picture Weil Felix test
Scrub typhus (tsutsugamushi disease)	*Rickettsia tsutsugamushi*	Various Asiatic-Pacific areas	Trombiculid mites (chiggers) *Trombicula akamushi* et al	Mites field rats and other small mammals	Intracellular	Clinical picture Weil Felix test
Q fever	*Coxiella burneti i*	Australia, North America Panama Europe Middle East, Africa China (?)	Rickettsiae present in certain ticks but no proved instance of tick transmission to man	Ticks cattle sheep goats, and probably certain wild animals	Intracellular	Isolate rickettsiae complement fixation and agglutination with Q rickettsial antigen no Weil Felix
Rickettsialpox	*Rickettsia akari*	Northeastern United States	Mite *Allodermanyssus sanguineus*	House mice (*Mus musculus*)	Intracellular (intranuclear)	Clinical picture isolate rickettsiae complement fixation
Trench fever	*Rickettsia quintana*	Europe	H[illegible] an body louse (*Pediculus hum*[illegible] *humanus*)	Man	Blood urine	Clinical picture no Weil Felix
			VIRUS DISEASES			
Yellow fever—urban	Virus	Central and South America, Africa	Mosquitoes (*Aedes aegypti*)	Man	Blood in early stages, liver parenchyma	Clinical picture in severe cases autopsy findings in mild cases isolate virus neutralizing antibodies
Yellow fever—jungle	Virus (same as above)	Central and South America Africa	Mosquitoes (*Haemagogus spegazzinii* et al in S A *Aedes simpsoni* et al in Africa)	Monkeys and other animals as yet undetermined	Blood in early stages liver parenchyma	
Dengue	Virus	Tropics and subtropics	Mosquitoes (*Aedes* spp)	Man?	Blood in early stages	Clinical picture leukopenia important
Sandfly fever	Virus	Tropics and subtropics	Sandflies (*Phlebotomus papatasi* and others)	Sandflies man?	Blood in early stages	Clinical picture leukopenia differential W B C.
Rift Valley fever	Virus	Africa	Mosquitoes (*Eretmapodites* spp and *Aedes* spp)	Cattle?	Blood	Complement fixation and neutralization tests
Colorado tick fever	Virus	United States	*Dermacentor Amblyomma* spp	Ticks?	Blood?	Complement fixation and neutralization tests
Bwamba fever	Virus	Uganda Africa	?	?	?	Neutralization tests

Table XI 1. Human Diseases Transmitted by Arthropods—Virus Diseases (Continued)

DISEASE	ETIOLOGIC AGENT	GEOGRAPHIC DISTRIBUTION	VECTOR	RESERVOIR	LOCATION OF ETIOLOGIC AGENT IN MAN	DIAGNOSTIC PROCEDURES
Western equine encephalomyelitis	Virus	United States, South Canada, Argentina	Mosquitoes (*Culex tarsalis* and others)	Probably wild and domestic mammals and birds	Central nervous system	
Eastern equine encephalomyelitis	Virus	United States, Canada, Mexico, Cuba, Panama, Dominican Republic	Mosquitoes (*Aedes sollicitans*, *Mansonia perturbans*)	Horses, pheasants, probably others	Central nervous system	
California encephalomyelitis	Virus	*San Joaquin Valley* California	*Mosquitoes* (*Aedes dorsalis*, *Culex tarsalis*)	*Horses and other mammals*	?	
Venezuelan equine encephalomyelitis	Virus	N. South America, Trinidad, Panama	Mosquitoes (probably *Aedes* sp. and *Mansonia* sp.)	Probably wild and domestic mammals and birds	Central nervous system	Isolate virus, complement fixation, neutralizing or hemagglutination-inhibition antibodies, pathology
St. Louis encephalitis	Virus	United States	Mosquitoes (*Culex tarsalis*, *C. pipiens*)	Probably wild and domestic mammals and birds. Perhaps man as well	Central nervous system	
Japanese B encephalitis	Virus	Japan, Okinawa, Guam, Korea, China, Manchuria and U.S.S.R. and probably much of Far East	Mosquitoes (*Culex tritaeniorhynchus*)	Man or birds?	Central nervous system	
Russian spring-summer encephalitis	Virus	U.S.S.R.	Ticks (*Ixodes persulcatus*, possibly others)	Unknown	Central nervous system	
Louping ill	Virus	England, Scotland, Czechoslovakia, White Russia	Tick (*Ixodes ricinus*)	?	Blood?	Isolate virus, complement fixation, neutralizing or hemagglutination inhibition antibodies, pathology
MISCELLANEOUS						
Enteric diseases, typhoid, bacillary and amebic dysentery, diarrheas, Asiatic cholera, certain helminthic infections		Differs in various regions	Houseflies (*Musca domestica*) et al. frequenting human excrement and food; mechanical transmission	Man	Intestines, etc.	Clinical picture, stool exam and culture
Human bots (myiasis)	*Dermatobia* spp.	American tropics	Flies, mosquitoes, bloodsucking arthropods	Various mammals, birds	Superficial layers of skin	Appearance of lesion, excision

three classes of the Phylum ARTHROPODA are represented in the list For example, the CRUSTACEA are represented by the minute *Cyclops*, certain species of which play host to *Dracunculus medinensis*, whereas others carry *Diphyllobothrium latum* Larger forms such as crayfish and crabs, harbor infective stages of *Paragonimus westermani*

A second major group, the ARACHNIDA, is represented by the ticks and mites, proved vectors of certain rickettsial viral, bacterial and spirochetal diseases

The third and by far the most important group of arthropods is the Class INSECTA (HEXAPODA), or true insects Here occur the majority of disease vectors Not all groups of insects, however, are equally fitted to serve in this capacity Of the 30 or more orders of insects known to science, only five are significantly involved in the dissemination of viruses bacteria or other disease producing organisms

1 The ORTHOPTERA (cockroaches and others)
2 The HEMIPTERA (true bugs)
3 The ANOPLURA (sucking lice)
4 The SIPHONAPTERA (fleas)
5 The DIPTERA (true flies, including mosquitoes)

Again within each of the above listed orders only certain families and, in many instances, only certain species are biologically adapted for the harboring and transmission of pathogenic forms Such adaptation, however, manifests itself in many ways, as illustrated by the following outline

Arthropods as Vectors of Disease
1 *Accidental* (e g typhoid by house fly)
  (*a*) On mouth parts
  (*b*) Through alimentary canal
  (*c*) On body legs and hairs
2 *Obligatory*
  (*a*) Propagative only parasites multiply but do not change in form or type (plague bacillus in gut of flea)
  (*b*) Developmental only parasites grow in size and change in structure but do not multiply (microfilariae in bodies of flies)
  (*c*) Cyclico propagative parasites both multiply and undergo developmental changes (malaria plasmodia in body of mosquito)

Special mention should be made also of transovarial transmission, by which the disease organism may pass into the egg of the infected arthropod and thus become capable of being transmitted by the succeeding generation The vector in this case becomes also a reservoir of the disease as do ticks in the transmission of Rocky Mountain spotted fever

Role of Arthropods as Direct Agents of Human Disease or Discomfort

All blood sucking vectors are more or less important as pests in their own right If, in addition to these, consideration is given to the blood suckers which are not vectors, and to the spiders, centipedes and stinging forms, as well as to various groups which live as parasites within tissues and cavities, the list of species capable of acting as direct agents of harmful or at least annoying conditions in man becomes exceedingly large Four classes of arthropods are here involved

1 Class ARACHNIDA (scorpions, spiders, ticks, mites)
2 Class PENTASTOMIDA (tongue worms)
3 Class CHILOPODA (centipedes)
4 Class INSECTA (HEXAPODA) (insects, many groups)

It will be noted that two of the above listed classes (ARACHNIDA and INSECTA), were also mentioned as containing vectors of disease

The particular role played by each group (or species) will be treated in its proper place

Pathologic conditions caused by these various arthropods may be classified as follows

1 Entomophobia
2 [illegible]
3 [illegible]
    (b) Stings (bees, wasps ants scorpions)
    (c) [illegible]
    (d) [illegible]
    (e) [illegible]
4 Infestat [illegible] iasis (beetles), scoleciasis (lepidopterous species)
5 Dermatoses (fleas lice, mites ticks and others)

Entomophobia This term refers to any of a number of psychic or nervous states in which the patient exhibits an abnormal fear or dread of the presence of arthropod forms In rare instances the services of a psychiatrist may be required

Accidental Injury to Sense Organs. Many practitioners have had the experience of removing an insect or parts thereof from the eye, ear or nasal passages of a patient The discomfort is usually mechanical in nature, although in some instances the insect produces an irritating secretion as well More serious is the presence of fly larvae in the eyes nose or sinuses Such larvae (or the eggs from which they hatch) must be deposited in or near the definitive location by the fly (See page 748)

Envenomization In a number of ways, insects and other arthropods are known to poison human beings, the degree of discomfort depending

Table XI.2 Envenomization (Including Allergies)

COMMON NAME	SCIENTIFIC NAME (OR GROUP)	DISTRIBUTION	IMPORTANT EFFECTS ON MAN	REMARKS
Mites				
Chiggers	*Eutrombicula alfreddugesi* and other trombiculid larvae	Tropics and warmer temperate regions	Intense itching dermatitis persistent purplish ecchymoses	Avoid by use of protective clothing dimethyl or dibutyl phthalate repellents
Cheese and flour mites	Several genera of ACARIDAE (TYROGLYPHIDAE)	Worldwide	Dermatitis allergic phenomena from contact with dead bodies of mites	Infestation usually limited to handlers of dry food products
Rat mites	*Ornithonyssus bacoti*	Worldwide	Dermatitis intense itching hemorrhagic areas	Infests persons who work or loiter in rat infested premises
Grain itch mites	*Pyemotes ventricosus*	Widespread	Dermatitis and fever	Infests threshers and persons who sleep on or work with straw
Ticks				
Soft ticks	*Ornithodoros* spp	All continents	Local and systemic reactions some species (*O coriaceus*) extremely venomous	Avoid rest houses rodent burrows, mountain homes
Hard ticks	*Dermacentor andersoni*	Western Canada, Western U S A.	Tick paralysis	Early removal of ticks very important otherwise usually fatal
	D variabilis	Eastern U S A., Pacific Coast	Tick paralysis	
	Ixodes spp	Widespread	Tick paralysis	
Black Widow Spiders	*Latrodectus mactans* *Latrodectus* spp	The Americas Widespread	Abdominal rigidity intense pain	10 ml calcium gluconate (10%) intravenously
Other venomous spiders	*Loxosceles reclusa*	N America	Necrotic lesion fever rash	Brown spider bite
	L laeta	S. America	Gangrenous spot	
	Lycosa raptoria	S America esp Brazil	Necrosis pain swelling	Necrotic arachnidism
Scorpions	Order SCORPIONIDA	Tropics and subtropics	Painful sting neurotoxin and hemolysin injected sometimes fatal	Ligature and cryotherapy helpful use antivenin if available other treatment empirical
Centipedes	Class CHILOPODA	Warmer regions	Painful bite local necrosis generalized symptoms	Give sedatives apply [illegible] on a [illegible] locally [illegible]
Insects				
Mayflies	Order EPHEMERIDA	Worldwide	Asthmatic paroxysms from inhalation of insect fragments	Desensitization perhaps feasible
Caddis flies	Order TRICHOPTERA	Worldwide	Asthmatic symptoms from inhalation of hairs and scales	Desensitization perhaps feasible
Kissing bugs (cone noses)	Fam REDUVIIDAE	Worldwide	Painful bites, with more or less local edema and inflammation	Symptoms vary with species may be due to Chagas disease
Blister beetles (and others)	Fam MELOIDAE Fam STAPHYLINIDAE Fam PAUSSIDAE	Worldwide Worldwide Worldwide	Severe blisters (from cantharidin) Delayed blistering effect	Symptoms result from crushing insects on skin Apply soothing lotions
Caterpillars (with urticating hairs and spines)	Order LEPIDOPTERA (several families)	Worldwide	Irritant rash and generalized symptoms on contact with hairs or spines	Codeine alkaline compresses useful supportive treatment [illegible] necessary
Bees, wasps, certain ants	Order HYMENOPTERA (several families)	Worldwide	Painful stings local swelling sometimes anaphylaxis (certain ants bite rather than sting)	Apply soothing lotions administer epinephrine subcutaneously for anaphylaxis

Table XI 3. Dermatoses of Arthropod Origin

COMMON NAME OF ARTHROPOD	SCIENTIFIC NAME (OR GROUP)	DISTRIBUTION	EFFECTS ON MAN	REMARKS
Itch Mites (scabies)	*Sarcoptes scabiei*	Worldwide	Burrows in skin causing chronic dermatosis (acariasis)	Transmitted by direct contact or by clothing, bedding. Eurax cream, Kwell ointment.
Hard Ticks	*Amblyomma* spp. *Hyalomma* spp. *Haemaphysalis leachi*	Widespread South Africa South Africa	Cause extreme annoyance	Protective clothing helpful. DDT effective against larval forms. Vectors of certain rickettsial diseases
Springtails	Order COLLEMBOLA (Several species)	Worldwide	Sharp bites, followed by pruritus	Ordinarily phytophagous. Introduced into houses (and hospitals) on garden vegetables and flowers
Lice				
Head lice	*Pediculus humanus capitis*	Worldwide	Hair becomes matted with fetid odor	Delousing spray or powders (DDT, lindane, etc.) see p. 774. Body louse vector of epidemic typhus, relapsing fever and trench fever
Body lice	*P. humanus humanus*	Worldwide	Reddish papules, pruritus followed by induration and pigmentation	
Pubic lice	*Phthirus pubis*	Worldwide	Intense irritation; attacks not necessarily limited to pubic region	
Bedbugs	*Cimex lectularius* *Cimex hemipterus* *Cimex (Leptocimex) boueti*	Worldwide Tropical and subtropical South America, Africa, New Guinea	Periodic blood-suckers; some persons suffer from bites, others immune to attack	No proved role in disease transmission (mechanical vectors under experimental conditions)
Fleas				
Human flea	*Pulex irritans*	Worldwide	Marked dermatitis frequent	Apply soothing lotions. Vectors of important disease agents. Avoid contact
Dog flea	*Ctenocephalides canis*	Worldwide	Marked dermatitis frequent	
Cat flea	*Ctenocephalides felis*	Worldwide	Marked dermatitis frequent	
Tropical rat flea	*Xenopsylla cheopis*	Spreading from tropics	Marked dermatitis frequent	
Other rodent fleas	*Xenopsylla* spp.	Widespread	Marked dermatitis frequent	
Chigoe flea (jigger)	*Tunga penetrans*	Tropical Africa and America	Burrows in skin, introduces tetanus, gas gangrene, other organisms	Remove flea aseptically. Dilute lysol bath before and after removal recommended
Flies (all types):				
Punkies	*Culicoides* spp.	Worldwide	Nodular inflamed swelling becoming vesicular	Attack in daytime; fierce biters. Transmit certain helminth infections
Black flies	*Simulium* spp.	Worldwide	Hemorrhagic punctures, pain, swelling, general discomfort	Vectors of onchocerciasis
Sandflies	*Phlebotomus* spp.	Widespread in warmer regions of the world	Stinging bite followed by itching whitish wheals	Night biters. Prefer ankles, wrists. Vectors of several diseases
Mosquitoes	Family CULICIDAE	Worldwide	Swelling, itching, annoyance according to susceptibility of individual	Over 1500 species, of various biting habits. Vectors of several diseases
Horse and deer flies	Family TABANIDAE (*Tabanus, Chrysops*)	Worldwide	Painful bite, no poisonous aftereffects	Daytime biters. Vectors of loiasis, tularemia
Snipe flies	Family RHAGIONIDAE	Europe, Australia, the Americas	Painful bite, no poisonous aftereffects	Daytime biters, few species attack man. Not vectors of disease
Stable flies (dog flies)	*Stomoxys calcitrans*	Worldwide	Painful bite, no poisonous aftereffects	Feeds to capacity in 3-4 minutes. May be mechanical vector of disease
	Stomoxys spp.	Africa	Painful bite, no poisonous aftereffects	(As above)
Tsetse flies	*Glossina* spp.	Africa	Painful bite, no poisonous aftereffects	Cyclical vectors of various trypanosomes of man and animals

upon the susceptibility of the individual as well as upon the species of arthropod concerned Hemolytic, hemorrhagic, neurotoxic and vesicating effects have been recorded Specific examples will be considered in connection with the discussion of particular taxonomic groups

It is not easy to separate the better known types of envenomization (bites stings) from reactions manifestly allergic in character Ordinarily a degree of discomfort more or less common to all exposed individuals is not regarded as allergic When, however, the symptoms are extremely severe, and especially if they occur in only a minority of the individuals exposed, the term is regarded as appropriate Asthmatic symptoms caused by the inspiration of fragments of mayfly wings are a case in point (Table XI 2)

Infestation by Insect Larvae. Not infrequently the human body plays host to insect larvae of different types, chiefly of the order DIPTERA This condition is termed *myiasis*, which means simply "being infested with flies" Some species, such as the Congo floor maggot, the Tumbu fly and the so called human bot fly are confirmed parasites and can live in no other way Others, such as the flesh flies and blue bottles, may develop either in nonliving organic matter or in living tissue A third group occasionally adapt themselves to the intestinal tract or to the genitourinary passages, where they cause varying degrees of irritation and distress These three types of parasitism are termed "specific," "semispecific" and "accidental" in the order named Very rarely the larvae of beetles (COLEOPTERA) have been recovered from man, in which case the term *canthariasis* is more appropriate The term *scoleciasis* is applied to the presence of lepidopterous larvae in the human intestinal tract

Dermatoses. Closely related to the irritation caused by insect bites are various skin conditions due either to this cause or to the actual presence of arthropods in the skin, as in the case of infection by *Sarcoptes scabiei* (Linn) the well known itch mite of man

Although a transient dermatitis may be evident in connection with the bite of one (or a few) blood sucking insects, a persistent dermatosis is usually the result of attack by large numbers over a considerable period This is particularly true in *pediculosis*, caused by prolonged harboring of the human louse, *Pediculus humanus* Linn

Specific types of dermatoses are described in detail in connection with the discussion of particular species groups Species and groups already listed under Envenomization Table XI 2 are not repeated in Table XI 3

Structure, Classification and Biology of Medically Important Arthropods

Characterization. The Phylum ARTHROPODA is the most highly evolved of all invertebrate groups Its members are characterized by a chitinous exoskeleton, a more or less marked segmentation of the body

both externally and internally, and the presence of several pairs of jointed appendages In such a vast group (well over half a million described species) it is not surprising that some forms fail to manifest all the characteristics listed Thus body segmentation is not evident in the ticks and certain larval forms, such as the maggots of flies, have no appendages at all Their life histories, however, furnish ample evidence for their inclusion with the rest

The five medically important classes will be discussed in turn

Class Crustacea

The members of this large group of aquatic arthropods are familiarly known as crabs crayfish, lobsters, shrimps, prawns, etc All species breathe by true gills and are characterized by the presence of two pairs of antennae and at least five pairs of legs The openings of their reproductive organs are usually far forward on the body (Fig XI 1)

Subclass Copepoda. These are small elongate, distinctly segmented forms with paired biramous appendages, six on the head and five on the anterior trunk region (Fig XI 1)

Two important parasites of man, *Diphyllobothrium latum* (broad tape worm) and *Dracunculus medinensis* (guinea worm), pass a portion of their life cycle in copepods, notably species of *Cyclops* and *Diaptomus* which acquire infection by swallowing microscopic stages of the parasites

Subclass Malacostraca. These are the larger CRUSTACEA The better known forms fall in the Order DECAPODA, certain species of which act as intermediate hosts for *Paragonimus westermani*, the lung fluke of man Species of marine crabs which migrate up fresh water streams, and less frequently fresh water crayfish are natural hosts in Korea and Japan various other fresh water crabs serve in a similar capacity in other areas (Fig XI 1)

Class Arachnida

This group, which includes the spiders, scorpions, ticks and mites, is of great medical importance Because of the many diseases capable of transmission by arachnids (especially the ticks) this class is discussed separately (pp 671–689)

Class Pentastomida (Linguatulida)

This group is composed of degenerate, wormlike parasites with neither circulatory nor respiratory organs The adults possess two pairs of hooks near the mouth, otherwise they are without appendages Their larvae however, bear two pairs of very short legs (Fig XI 1)

As a rule the adults live in the respiratory passages of carnivorous reptiles, birds and mammals the eggs being discharged in the sputum or nasal mucus The intermediate host usually an herbivore, takes up the eggs in food or water The larvae emerge in the intestine migrate to the liver, spleen lymph nodes or lungs and there become encapsulated From the nature of the life cycle it is evident that man is more likely to function as an intermediate than as a definitive host At least four species have been recorded from human tissue

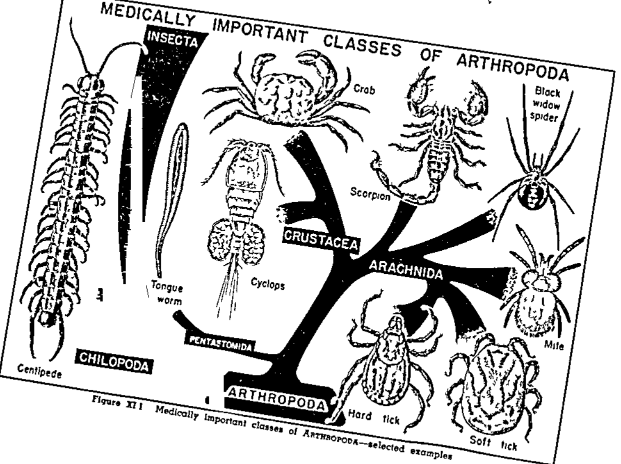


Figure XI 1 Medically important classes of ARTHROPODA—selected examples

Class Chilopoda

The centipedes are elongate arthropods with a *conspicuous pair of* legs on each segment of the body They have poison glands in the claws of the first pair of leglike appendages and by injecting this material into their prey (insects and other small animals) cause immediate paralysis or death Only a few however have jaws sufficiently strong to penetrate the skin of man Two American species *Scolopendra heros* and *S morsitans* are large forms (4 or more inches in length) capable of inflicting painful bites Certain tropical species among them *Scolopendra gigantea* (about 10 inches in length) are reputed to be quite poisonous Persons are usually bitten in bed or when putting on clothing in which centi When pinched or impeded they bite

here is intense fiery pain at the site of the bite Usually the immediate pain diminishes within an hour much like the sting of a honey bee and no further symptoms ensue In some cases the area near the wound may become inflamed swollen and tender it may remain tender and mildly painful for a few weeks Occasionally regional glandular enlargement headache vertigo fever and vomiting occur Centipede bites generally are not considered very serious to man Only one apparently authentic case is recorded in the literature several decades ago in which a centipede bite was fatal to a human—a child who was bitten by *S subspinipes* in the Philippines Treatment consists of administration of codeine or local palliatives for relief of pain Injection of a local anesthetic at the site of the bite relieves the pain quickly Application of an ice pack may also afford relief Dilute ammonia applied locally has been recommended

Class Diplopoda

Millipedes sometimes confused with centipedes belong to a distinct class the DIPLOPODA They are characterized by the presence of *two*

portance though collectors have reported irritation of the skin from handling the living specimens Some of the smaller species have been found in the digestive and urinary tracts of man Millipedes may serve as intermediate hosts of *Hymenolepis diminuta* the rat tapeworm which is occasionally found in humans

Class Insecta (Hexapoda)

The vast majority or arthropod borne diseases are insect borne This is not strange when one considers that the Class INSECTA alone is vastly larger than all the other classes put together and that there are few places on the earth s surface where man is not in constant and intimate association with insect forms For information concerning the medically important groups see pages 689 757

72

The Class Arachnida

Revised by Kenneth L. Knight

The ARACHNIDA constitute one of the more important classes of arthropods. In typical forms, the head and thorax are fused together, forming a cephalothorax. Adults normally possess four pairs of legs. The class includes at least nine distinct orders but only three, the SCORPIONIDA, ARANEIDA and ACARINA, are of medical importance. These will be discussed in turn.

The Order Scorpionida (Scorpions)

Scorpions are found largely in the warmer regions of the world. They have exceedingly large *pedipalps*, furnished with stout pinching claws. The cephalothorax is compact, but the abdomen is conspicuously segmented. The anterior portion of the abdomen is broad, the posterior five segments are much narrowed, forming a conspicuous tail at the tip of which is a bulblike enlargement bearing the poisonous sting. It is this sting and not the anterior claws which is dangerous to man. Some species carry the tail over the back in a threatening attitude as they run about, in others, it merely drags along behind. Approximately 650 species are known, but only a limited number inject sufficient poison to make their stings a matter of concern (Fig. XI 1).

Centruroides suffusus Pocock is credited with having caused the death of some 1600 persons, mostly children, in the State of Durango, Mexico, over a period of 36 years. At least four other species of the same genus are regarded as capable of inflicting fatal stings. One hundred forty five deaths were reported from 1328 stings (mostly children) in Bello Horizonte, Brazil. *Tityus serratulus* being probably the chief offender. The Egyptian species, *Buthus quinquestriatus* Hemprich and Ehrenberg, is exceedingly dangerous, the mortality rate among children [illegible] Trinidad, [illegible] Tropical [illegible] largest species are not always the most poisonous.

Life History. Scorpions are nocturnal, feeding on spiders and larger insects which they seize with their claws (pedipalps) and sting to death During the day they lie hidden beneath debris of all kinds such as loose stones or bits of bark, as well as under buildings and lumber piles Those which invade houses may hide in shoes or clothing as day approaches

Symptoms. Most ground scorpions inject a primarily hemolytic toxin, which is only rarely, if ever, fatal The venom produces mainly a local reaction which consists of a sharp burning sensation and a pronounced swelling, with or without discoloration or necrosis The inflammation and pain may travel some distance from the site of the sting Some scorpions, largely characterized by being nonburrowing inject a venom which is primarily neurotoxic (*Centruroides, Prionurus, Buthus, Euscorpius, Scorpio* and *Tityus*, for example) and which may cause death This venom produces generalized reactions characteristically consisting of hypersensitization of the sting site (but with little swelling or discoloration), nausea, tightness of throat muscles, salivation, sweating, partial paralysis of the tongue, abdominal cramps, vomiting, restlessness cyanosis, convulsions and, rarely, death following respiratory paralysis

Treatment. All scorpion stings should be treated by a physician as *soon as possible, since susceptibility to scorpion poison is extremely* variable Current first aid procedures no longer call for incision and suction Instead, an arrestor (tourniquet) and cryotherapy with ethyl *chloride or crushed ice in water are employed An arrestor should be* applied immediately, just proximal to the sting Put a piece of ice on the site while preparing a suitable vessel of crushed ice and water Sub*merge the affected member well above the tourniquet in the ice water* for five minutes before removing the tourniquet Leave the appendage in iced water for at least two hours without a tourniquet

Clinical treatment consists of the administration of glucose followed by insulin Antivenins are available for some of the more dangerous scorpion poisons Artificial respiration and other symptomatic treatment measures may be indicated Drugs which are respiratory depressants should not be employed

Whip Scorpions

"Whip scorpions" belong to the PEDIPALPIDA They are distinguished

roon" This secretion may be irritating to sensitive skin, [illegible]
are quite harmless, in spite of widespread opinion to the contrary

The Order Araneida (Spiders)

Spiders constitute a large group at least 30 000 forms have been described These arthropods have a head and thorax joined into a single body region the cephalothorax which in turn is joined to the unsegmented abdomen by a rather slender pedicle The *chelicerae* or jaws each contain a poison gland which opens near the tip of the second (distal) segment Pedipalps of six segments precede the four pairs of legs and may give the impression that five pairs of legs are present A spider's "silk" is produced from three or four pairs of spinnerets located near the tip of the abdomen on the ventral side

Although spiders are venomous only a few species are actually dangerous to man Medical interest centers in two groups termed respectively *tarantulas* and *black widows* which may be distinguished as follows

Tarantula Group

The term "tarantula as employed in Europe relates specifically to *Lycosa tarentula* (Family LYCOSIDAE) The bites of LYCOSIDAE however are not very serious They have never been shown to cause death in man and with the exception of a few American species cause no great discomfort The Russian tarantula *Trochosa singoriensis* is much feared but the fear is probably without foundation

In America the term "tarantula" is loosely used for any of the larger hairy spiders most of which fall in the superfamily AVICULARIOIDEA They are found in Central and South America as well as in the southern and southwestern United States They may be distinguished from all other spiders by the fact that their chelicerae are paraxial that is they both extend forward and operate vertically with a downward stroke rather than against one another from opposite sides (diaxial articulation) Members of the genus *Eurypelma* are typical With their heavy bodies and leg spread of five or more inches they excite much apprehension but the effect of their bite is trivial *Sericopelma communis* the "black tarantula of Panama is probably the most venomous of the group

Sometimes confused with these American tarantulas are certain large spiders (Family HETEROPODIDAE) found frequently in shipments of tropical fruit particularly bananas They may be recognized by their smoother bodies longer legs and diaxial jaws *Heteropoda venatoria* Koch is the species most commonly seen Its bite is painful but not serious

Black Widow Group

Of much greater importance than the three foregoing families is the family THERIDIIDAE This group includes a number of rather small dark spiders falling in the genus *Latrodectus* the bites of which are extremely poisonous and sometimes fatal Best known of this group is *Latrodectus mactans* (Fabricius) a cosmopolitan species found in the warmer regions

of the world It is believed by some that this black widow spider consists of two separate species *L mactans*, occurring in the New World (not north of Maryland, Indiana, Wyoming, Utah and central California in the United States), and *L curacaviensis* (Muller) This latter species ranges in the Americas from Argentina to Canada, although it more commonly occurs in the temperate zones The cosmopolitan brown widow spider, *L geometricus* Koch, has occasionally been found in Florida The Russian spices, *L erebus*, also called "Kara kurt' or "black wolf," is quite as dangerous as the American species Other members of the genus occur in southern Europe, the Middle East, Australia, New Zealand the Philippines, Madagascar, South and West Africa and Brazil

The widow spiders are easily recognized (Fig XI 1) by the black brown or gray globose abdomen and the red, orange, yellow or white hourglass markings on the underside of the abdomen Immature specimens and males have additional markings, not found in the adult females, on the upper surface of the abdomen and sometimes on the legs Mature females are about one half inch long not including the legs, the males are somewhat smaller

Life History. Black widows are found largely in cellars, privies manholes and culverts, or under rocks bridges or in hollow logs Here they spin a loosely woven coarse, irregular web in which insects and other small prey are captured After mating the female lays 300 to 400 eggs enclosed in a dense ball of silk nearly three-eighths of an inch across (The name "black widow" is derived from the fact that the males are frequently devoured by the females after mating) The young spiders hatch in three or four weeks and scatter over the web At first they are light tan, but become darker with succeeding molts A single female may construct as many as nine successive egg sacs, though the fertility of the latter batches may be somewhat reduced, owing to exhaustion of sperm Spiders hatching in midsummer may complete their development the same season, but hibernation in all stages is not uncommon The males pass through five instars, the females seven or eight

The males seldom or never bite, and it would not be important if they did so, as extracts prepared from mature males have been found less than one fortieth as poisonous as those prepared from females Female venom, on the other hand, has been shown to be 15 times as potent, on a dry weight basis, as that of *Crotalus albicans*, the prairie rattlesnake It differs chemically from snake venom, however, being neither an alkaloid nor a glucoside but a toxalbumin

Black widow spiders ordinarily bite only legitimate prey, but when frightened or injured, strike in self defense A female, guarding her egg sac, is particularly vicious, and since the under side of privy seats is a favorite location for egg laying, it follows that a majority of recorded bites are received in outhouses and latrines the male genital organs being the parts most commonly attacked

Symptoms of Spider Poisoning (*Arachnidism*). The spider bite itself is not always felt, or if so, is no more painful than a pin prick Two tiny red spots occasionally may be seen, and there may be some local swelling, but the more serious symptoms are general in character Within

ten minutes there is usually cramping pain the distress involving suc-
cessively the abdomen legs chest and back At the end of an hour
the patient may be writhing in agony All of the larger muscle groups
show marked rigidity the [illegible] especially marked in the
[illegible]
[illegible] simulate perforated peptic
[illegible] colic angina pectoris tetanus food poisoning and other conditions
[illegible] appendicitis acute pancreatitis peritonitis
Incorrect diagnoses may subject patients suffering from arachnidism to
unnecessary surgical procedures In cases in which an incision has been
made the intestine has been found to be extremely contracted and
spastic (This may result in paralytic ileus) Acute symptoms persist
from 12 to 48 hours These may include elevation of temperature and
blood pressure as well as increased spinal fluid pressure Conversely in
some patients the temperature pulse and blood pressure [illegible]
normal and shock ensues There is [illegible]
excessive persp[illegible]
may be chill[illegible]
of the feet [illegible]
4 per cent of [illegible] end in death When [illegible] it is reported that
extremities however symptoms are usually less severe When the bites are on the

Treatment. If possible hospitalization should be accomplished in
order to ensure adequate nursing care The treatment of choice is in-
travenous administration of 10 ml of 10 per cent calcium gluconate
Hydrotherapy in the form of hot bath or hot packs is beneficial When
relief of muscle spasm and pain is not obtained with calcium gluconate
neostigmine methylsulfate or physostigmine given with atropine may
be effective Morphine usually provides clinical relief however since
L mactans venom contains a neurotoxin the use of drugs with a de-
pressant effect on the respiratory center is not indicated A number of
other drugs for example myanesin (Tolserol) epinephrine and the
corticosteroids reportedly have been useful in therapy of this venom
poisoning

A specific antivenin which is commercially available reduces the
severity relieves the symptoms and speeds recovery from black widow
spider poisoning if given soon after the patient was bitten Since the
antivenin is prepared from the serum of horses hyperimmunized to
the venom testing for horse serum sensitivity must be made before use
Most cases of black widow spider bite respond satisfactorily to the ad-
ministration of calcium gluconate or to some of the other drugs listed
above Therefore use of the antivenin may be reserved for selected cases
of venom poisoning Local treatment of the site of the bite has not
been found helpful

Other Spiders

An altogether different spider *Glyptocranium gasterocanthoides*
Nicolet an orb weaver of the family ARGIOPIDAE is regarded in Peru
Chile and Argentina as particularly venomous
Yet another spider *Loxosceles laeta* (Nicolet) is the causative [illegible]

of "gangrenous spot" or cutaneous arachnidism of Chile, Uruguay and other South American countries. The bite is followed by burning, erythema, edema, and the formation of a blister. The blister ruptures and the area becomes gangrenous; the eschar is sloughed off and a superficial ulcer is formed that may be as much as 15 cm across. Healing of the necrotic tissue takes place very slowly. It is believed that *L. reclusus* Gertsch is probably responsible for a somewhat similar condition that has been reported on a number of occasions following the bite of a "brown spider" in Missouri, Illinois, and in the southern and southwestern United States.

Jointed Spiders. The jointed spiders, also called sun spiders or wind scorpions, fall into the order SOLPUGIDA. They differ from true spiders in having the abdomen segmented and more broadly joined to the cephalothorax. Their chelicerae, which are two-segmented, are large, powerful, and capable of inflicting a painful bite, but the effect is transitory, as no poison glands are present. Because of the depth of penetration, the possibility of secondary infection, however, should not be overlooked. The group occurs largely in desert, tropical, and subtropical regions. Solpugids are chiefly nocturnal.

The Order Acarina (Ticks and Mites)

Revised by Carroll N. Smith

Members of this order can, as a rule, be readily distinguished from other ARACHNIDA, as well as from insects, by the general absence of body segmentation. A head is lacking and, with the exception of some adult mites, there is a strong fusion of thorax and abdomen with no external sign of demarcation. Wings or antennae are never present. As with spiders and scorpions, the adults have four pairs of legs, but the larvae have only three pairs (occasionally less in some mites). The two major groups can be best discussed separately.

The Superfamily Ixodoidea (*Ticks*)

The ticks are further characterized in general as follows. Eyes, when present, are simple. The mouth parts consist of a pair of dorsal cutting organs, the *chelicerae*; a ventral, characteristically toothed *hypostome* for anchoring the tick to its host; and paired *palpi* lateral to the mouth. The mouth consists of a chitinous ring lying at the base of, and between, the chelicerae and the hypostome.

The superfamily IXODOIDEA is ordinarily divided into two family groups, the ARGASIDAE and the IXODIDAE. These may be separated on the basis of a single structure, the *scutum*, which is lacking in the ARGASIDAE in all stages (soft ticks) and present in the IXODIDAE in all

stages (hard ticks) In the ixodid female the scutum covers only the anterior part of the dorsal surface in the male it covers most of the dorsal surface The two groups are further characterized by ventral mouth parts and only slight sexual dimorphism in the argasid ticks and by mouth parts that project in front of the body when viewed dorsally and marked sexual dimorphism in the ixodid ticks (Figs XI 1 XI.2 XI 3)

The Family Ixodidae *(Hard Ticks)* The family IXODIDAE consists of at least ten well defined genera composed of over 300 species Five genera are of special importance to man These are *Dermacentor Amblyomma Rhipicephalus Haemaphysalis* and *Ixodes* Species of the genus *Amblyomma* are chiefly tropical or subtropical in their distribution The other genera have representatives that are worldwide or nearly so in their range

Relation to Man Numerous species of ixodid ticks are of the greatest medical importance as reservoirs or vectors of agents of disease which affect man and the lower animals Among the agents transmitted to man are rickettsiae viruses bacteria and others whose nature is unknown The rickettsial diseases of man are American spotted fever fievre boutonneuse (including Kenya typhus South African tick bite fever and Indian tick typhus) Siberian tick typhus North Queensland tick typhus and Q fever Colorado tick fever and Russian spring summer encephalitis are caused by viruses and tularemia is a bacterial disease The agents of Bullis fever a disease which as yet is not definitely known to be tick borne and of tick paralysis have not been discovered but the latter disease is believed to be caused by a toxin Methods of transmission include tick bite and contact of tick feces fluids or crushed tick tissues with the skin The tick borne diseases of animals are numerous and result in vast eco-

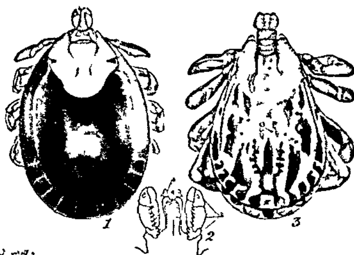


Figure XI.2 1 Female Dermacentor andersoni 2. Mouthparts showing (a) hypostome (b) chelicerae (c) palps 3 Male (Strong Stitt s Diagnosis Prevention and Treatment of Tropical Diseases The Blakiston Co)

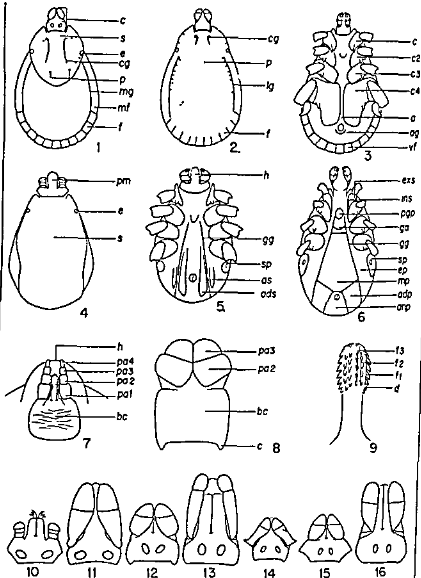


Figure XI 3 Morphology of adult ticks 1 *Dermacentor* female dorsal view c capitulum cg cervical groove e eye f festoon mf marginal fold mg marginal groove p punctations s scutum 2 *Dermacentor* male dorsal view cg cervical groove f festoon lg lateral groove p punctation 3 *Dermacentor* male ventral view a anus ag anal groove c1 coxa I (bifid) c2 coxa II c3 coxa III c4 coxa IV vf ventral festoon 4 *Boophilus* male dorsal view e eye pm piercing mouth parts s scutum. 5 *Boophilus* male ventral view as accessory shield ads adanal shield gg genital groove h hypostome sp spiracular plate 6 *Ixodes* male ventral view adp adanal plate anp anal plate ep epimeral plate exs external spur on coxa I ga genital aperture gg genital groove ins internal spur mp median plate pgp pregenital plate sp spiracular plate 7 *Ornithodoros* (ARGASIDAE) ventral view bc basis capituli h hood pa1 palpal article 1 pa2 palpal article 2 pa3 palpal article 3 pa4 palpal article 4 8 *Dermacentor* male

nomic losses, moreover, heavy infestation may result in severe anemia or death, even in large animals, from blood loss alone

Life History All species of ixodid ticks pass through four stages egg, larva, nymph and adult The eggs are deposited on the ground where, after varying lengths of time, they hatch, giving rise to hexapod (six legged) larvae which soon seek a blood meal Some species show marked host specificity, others use a wide variety of hosts In multiple host ticks the engorged larvae drop from the host after several days of feeding and seek a cool place where they remain until molting takes place The resulting octopod (eight legged) nymphs then feed on a second host, again drop to the ground and await molting The ticks emerge from this second molt as adults, males and females An interval of a week to ten days is required for engorgement of the female during which time mating takes place This life cycle normally requires from a few weeks to two or more years, according to the species and host availability The number of eggs also varies greatly A maximum of 18 497 has been recorded for a single *Amblyomma maculatum* After egg laying is completed the female dies Some ixodid ticks for example, the southern cattle tick *Boophilus annulatus* (Say), do not drop from the host between feedings Such ticks are designated as one host ticks

The Family Argasidae (Soft Ticks). This family consists of four genera *Argas*, *Otobius*, *Antricola* and *Ornithodoros*

The genus *Ornithodoros* is by far the largest and most important of the four and contains approximately 50 species A large number of these will feed on man

Relation to Man *Argas persicus* (Oken), a widely distributed species of soft tick, is a common vector of fowl spirochetosis and occasionally feeds on man Some other species which are reported to bite man are *Argas brumpti* Neumann, *A reflexus* (Fabr) and *A mianensis* Brumpt The genus *Antricola* is of no importance to man, but the genus *Otobius* contains the widely distributed spinose ear tick of cattle a species which is occasionally found in the human ear In the genus *Ornithodoros* at least 12 species are known vectors of relapsing fever spirochetes and others are under suspicion on epidemiologic grounds (see Relapsing Fever, page 107) In addition some are efficient experimental vectors of the American spotted fevers *Ornithodoros turicata* (Duges) and others of this genus are capable of transmitting relapsing fever spirochetes to their progeny through the egg stage (transovarial transmission) Some species of *Ornithodoros* transmit relapsing fever spirochetes by bite, but the secretions of both salivary and coxal glands are media of transmission in *O moubata* (Murray), the eyeless tampan, which is an exceedingly important vector of relapsing fever in Africa

Some soft ticks, notably *Ornithodoros coriaceus* Koch, the "pajaro-

---

dorsal view *bc* basis capituli *c* cornu *pa2* palpal article 2 *pa3* palpal article 3 9 Hypostome of *Amblyomma* *f1*, file 1 *f2* file 2 *f3* file 3 *d* a single denticle 10 to 16 Typical capitula (Ixodidae) females dorsal view 10 *Boophilus* 11 *Ixodes* 12 *Dermacentor* 13 *Amblyomma* 14 *Haemaphysalis* 15 *Rhipicephalus* 16 *Hyalomma* (Courtesy Dr R. A. Cooley Rocky Mountain Laboratory U S P H S)

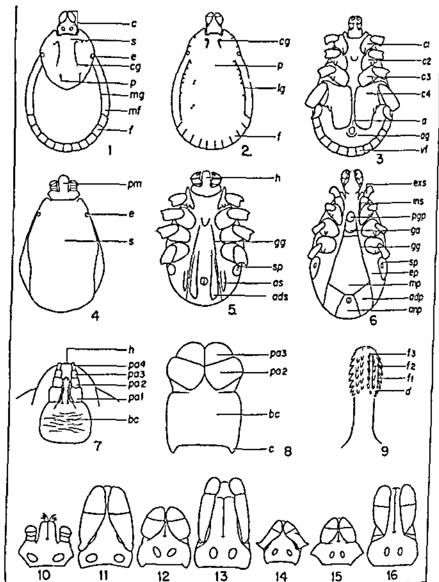


Figure XI 3 Morphology of adult ticks 1 *Dermacentor* female dorsal view *c* capitulum *cg* cervical groove *e* eye *f* festoon *mf* marginal fold *mg* marginal groove *p* punctations *s* scutum. 2 *Dermacentor* male dorsal view *cg* cervical groove *f* festoon *lg* lateral groove *p* punctation 3 *Dermacentor* male ventral view *a* anus *ag* anal groove *c1* coxa I (bifid) *c2* coxa II *c3* coxa III *c4* coxa IV *vf* ventral festoon. 4 *Boophilus* male dorsal view *e* eye *pm* piercing mouth parts *s* scutum. 5 *Boophilus* male ventral view *as* accessory shield *ads* adanal shield *gg* genital groove *h* hypostome *sp* spiracular plate 6 *Ixodes* male ventral view *adp* adanal plate *anp* anal plate *ep* epimeral plate *exs* external spur on coxa I *ga* genital aperture *gg* genital groove *ms* internal spur *mp* median plate *pgp* pregenital plate *sp* spiracular plate 7 *Ornithodoros* (ARGASIDAE) ventral view *bc* basis capituli *h* hood *pa1* palpal article 1 *pa2* palpal article 2 *pa3* palpal article 3 *pa4* palpal article 4 8 *Dermacentor* male

nomic losses, moreover, heavy infestation may result in severe anemia or death, even in large animals, from blood loss alone

Life History All species of ixodid ticks pass through four stages egg, larva, nymph and adult The eggs are deposited on the ground where, after varying lengths of time, they hatch, giving rise to hexapod (six legged) larvae which soon seek a blood meal Some species show marked host specificity, others use a wide variety of hosts In multiple host ticks the engorged larvae drop from the host after several days of feeding and seek a cool place where they remain until molting takes place The resulting octopod (eight legged) nymphs then feed on a second host, again drop to the ground and await molting The ticks emerge from this second molt as adults, males and females An interval of a week to ten days is required for engorgement of the female, during which time mating takes place This life cycle normally requires from a few weeks to two or more years, according to the species and host availability The number of eggs also varies greatly A maximum of 18 497 has been recorded for a single *Amblyomma maculatum* After egg laying is completed the female dies Some ixodid ticks, for example, the southern cattle tick, *Boophilus annulatus* (Say), do not drop from the host between feedings Such ticks are designated as one host ticks

The Family Argasidae (Soft Ticks). This family consists of four genera *Argas, Otobius, Antricola* and *Ornithodoros*

The genus *Ornithodoros* is by far the largest and most important of the four and contains approximately 50 species A large number of these will feed on man

Relation to Man *Argas persicus* (Oken), a widely distributed species of soft tick, is a common vector of fowl spirochetosis and occasionally feeds on man Some other species which are reported to bite man are *Argas brumpti* Neumann, *A reflexus* (Fabr) and *A miniensis* Brumpt The genus *Antricola* is of no importance to man, but the genus *Otobius* contains the widely distributed spinose ear tick of cattle, a species which is occasionally found in the human ear In the genus *Ornithodoros* at least 12 species are known vectors of relapsing fever spirochetes, and others are under suspicion on epidemiologic grounds (see Relapsing Fever, page 107) In addition, some are efficient experimental vectors of the American spotted fevers *Ornithodoros turicata* (Duges) and others of this genus are capable of transmitting relapsing fever spirochetes to their progeny through the egg stage (transovarial transmission) Some species of *Ornithodoros* transmit relapsing fever spirochetes by bite, but the secretions of both salivary and coxal glands are media of transmission in *O moubata* (Murray), the eyeless tampan, which is an exceedingly important vector of relapsing fever in Africa

Some soft ticks, notably *Ornithodoros coriaceus* Koch, the "pajaro

dorsal view *bc* basis capituli *c* cornu *pa2* palpal article 2 *pa3* palpal article 3 9 Hypostome of *Amblyomma* *f1*, file 1 *f2* file 2 *f3* file 3 *d* a single denticle 10 to 16 Typical capitula (Ixodidae) females dorsal view 10 *Boophilus* 11 *Ixodes* 12 *Dermacentor* 13 *Amblyomma* 14 *Haemaphysalis* 15 *Rhipicephalus* 16 *Hyalomma* (Courtesy Dr R A Cooley Rocky Mountain Laboratory U S P H S)

ello" of California and Mexico are dangerous because of their bi alone The bite of the "pajaroello" is extremely venomous and in son areas is reported to be more dreaded than the bite of a rattlesnake

Pasteurella tularensis can be transmitted experimentally by *O mouba* (Murray) but the infection ultimately proves fatal to the tick Stage stage and transovarial transmission of *Coxiella burnetii* by the same ti also has been demonstrated

Life History Biologically, ticks of the genus *Ornithodoros* th far studied are characterized by rapid feeding (exceptions in the lar stage of some species) multiple nymphal stages and longevity The feed on both warm blooded and cold blooded animals As a rule a com plete blood meal is necessary prior to each molt but in some specie both larval and first nymphal "skins" are shed after the larval feedin without an additional blood meal This phenomenon occurs only i species whose larvae require several days to engorge

In contrast to the one nymphal stage which is constant in ixodid tick the number of nymphal stages in the argasid ticks may vary with th *several species and even within the species In O hermsi a minimum o two nymphal stages and a maximum of four have been observed* wherea in *O coriaceus* the number varies from three to six There is a definit tendency for males to mature earlier than females for example in *O turicata* (Duges) following the third nymphal molt numerous males an a few females appear following the fourth nymphal molt a few male and many females appear and the few remaining ticks that require fifth nymphal molt are all females

[illegible] or afte

species notably *O nicollei* Mooser there is a tendency to oviposit second time without further feeding The number of eggs at a single oviposition varies with the species as few as 20 have been observed i *O stageri* Cooley and Kohls and more than 700 in *O rostratus* Aragao

The size varies widely The adult of *O normandi* Larrousse a Tunisian species is only 3 mm long whereas the engorged female of *O delanoe acinus* Whittick *from British Somaliland* reaches a maximum of 27 mm With the exception of the larvae of some of the bat ticks host specificity is not marked For example *O capensis* Neumann normally a parasite of certain marine birds feeds readily on man and on laboratory animals

Tick Paralysis This condition occurs not infrequently as a result of the bites of female ticks of the species *Dermacentor andersoni* (wood tick) and *D variabilis* (dog tick) The nymph of *Amblyomma a ieri canum* (lone star tick) and the adult of *A maculatum* and of *Ixodes holocyclus* have also been incriminated

The disease is probably produced by the introduction of a toxin con tained in the salivary secretion of the ticks *The exact origin* within the body of the tick of this toxin referred to by some workers as ixovotoxin is not known Possibly it is derived from the eggs or saliva or both It *has been shown conclusively* that tick paralysis is not a bacterial or viral disease

Both neuromuscular and central nervous system paralysis result from tick toxin There is a sudden onset with ataxia, asynergia, weakness, headache and paresthesia, and an ascending frequently flaccid, motor paralysis, usually bilaterally symmetrical, which in some cases may progress to a fatal conclusion in a few days Reflexes of affected parts may be hypoactive or absent, paralysis may involve the organs of respiration and the heart Constitutional symptoms are usually mild, and the temperature ordinarily is normal or slightly elevated Convulsions occasionally occur Children are far more commonly involved than adults The clinical entity is usually associated with tick attachments on the head, back of the neck or over the spinal column Careful examination may be required to detect ticks attached to the scalp and hidden by the hair, or those located in the ears, axillas, beneath the breasts, in gluteal folds, or in the groin and perineum Dramatic improvement usually is observed within a few hours following removal of the ticks, and the symptoms disappear completely within a few days Patients without marked paralysis and whose symptoms do not progress in severity after the first day are reported as well

The spinal fluid of affected individuals shows no abnormalities Tick paralysis is frequently mistaken for poliomyelitis and peripheral neuritis A similar condition occurs in lower animals and can be induced in experimental hosts such as the woodchuck, hamster, ground squirrel and dog but rats and mice seem to be immune

Avoidance of Tick Bites. Tick infested areas should be avoided, if possible, especially during spring and summer When entering such areas necessarily full length clothing and high laced boots, leggings, puttees or socks enclosing the trouser legs should be worn If the trousers are tucked into the socks or leggings and the shirt is tucked into the trousers the ticks usually will crawl to the neck Here their movements will b felt and they can be removed before they can attach Frequently tick do not attach immediately, and, after being exposed to them, one shou remove his clothing and make a careful inspection of his body with t aid of another individual In some infections the severity of the dise possibly may be reduced by early removal of attached ticks For chem methods of preventing tick attachments, see the tick repellents listed Table XI 10, page 772

Removal of Attached Ticks. A drop of chloroform, carbon t chloride ether benzene, tincture of iodine or spirits of turpentin the tick or petrolatum rubbed over it, will facilitate removal o ectoparasites Ticks should then be detached by gentle traction forceps or a suitable instrument, being certain to remove the tick without detaching the capitulum ("head") from the body Unles with care the "head," which is anchored by the recurved hooks armed hypostome will remain lodged in the skin and may pro severe lesion Apply tincture of iodine to the site of the bite after of the tick Touching the tick with the lighted end of a cigaret times causes them to release their attachment If the hands h ly contacted the tick during removal, wash them thorou the tick secretions may be infective

Confusion of Arthropod Bites with other Lesions of the Skin Reactions to attachments or bites of ticks chiggers mosquitoes and unidentified arthropods usually consist of a dense dermal infiltrate characterized by large numbers of eosinophilic leukocytes plasma cells and histiocytes They may be mistaken for Hodgkins disease mycosis fungoides atypical lymphoblastoma histiocytoses and the heterogeneous group of eosinophilic granulomas The lesions are often associated with pseudoepitheliomatous hyperplasia which may be confused with squamous cell carcinoma however the association with an eosinophilic dermal infiltrate and with epidermal inclusion cysts provides helpful differential clues

The reaction to the bites of arthropods may persist for many months and generally no appreciable difference is noted in the histologic reaction in lesions lasting from three weeks to two years A single cutaneous lesion with a histologic picture suggestive of Hodgkins disease or another lymphoblastoma should always be suspected as having been caused by the bite of an arthropod until conclusively proven otherwise The history of an insect bite may not be volunteered after a lapse of many months

Acarina Other Than Ticks *(Mites)*

More than 200 families of mites have been described The species comprising most of these families are free living but a few are parasites of plants or animals

The known parasitic species found on animals exhibit different degrees of parasitism Some are parasitic in all active stages (scabies mites) some only during the larval stage (chiggers) some are fortuitous parasites (cheese mites) still others such as the rare *Holothyrus coccinella* Gervais produce harmful effects by means of an irritant poisonous fluid

The mites affecting man may be considered in three groups (1) species which may cause a dermatitis (DERMANYSSIDAE PYEMOTIDAE, ACARIDAE and DEMODICIDAE (2) the chiggers larval mites of the family TROMBICULIDAE many of which may cause a dermatitis and some of which are vectors of the rickettsiae of scrub typhus (tsutsugamushi) (3) the itch mite *Sarcoptes scabiei* (SARCOPTIDAE)

Dermanyssidae *Ornithonyssus bacoti* (Hirst) (formerly treated under the genera *Bdellonyssus* and *Liponyssus*) the tropical rat mite occurs associated with rodents throughout the world It is frequently troublesome to humans living on rodent infested premises The bite is usually irritating and may even cause a painful dermatitis The tropical rat mite has been found naturally infected with murine typhus rickettsiae in China and the United States but epidemiologic evidence indicates that this mite is of negligible importance in the spread of the disease The tropical rat mite serves as the intermediate host of *Litomosoides carinii* a filarial nematode parasite of rodents and has been found capable of the experimental transmission of the plague bacillus and of rickettsial pox This mite is a serious pest of laboratory animals

Ornithonyssus sylviarum (C & F) the northern fowl mite occasionally bites man and has been found to be infected with western equine

encephalitis in California and with the Newcastle disease virus of chickens in Iowa It is to be found throughout the temperate regions, being parasitic on domestic fowls and many wild birds

Dermanyssus gallinae (De Geer), the chicken mite, is primarily a pest of chickens, but also parasitizes many species of wild birds, including pigeons, and also domesticated birds This species sometimes bites man, causing mild dermatitis and itching and ingesting blood It has been found naturally infected with the St Louis encephalitis virus It is widespread throughout the world

Allodermanyssus sanguineus (Hirst), the mouse mite, was described as a parasite of rats in Egypt (Fig XI 4) It has been demonstrated to be capable of transmitting a relatively mild rickettsial disease to mice that is known as rickettsialpox This species has been found naturally infected with *Rickettsia akari*, the etiologic agent of rickettsialpox, and is believed to have been responsible for human cases of this disease which have occurred in the northeastern United States (see page 91)

Pyemotidae (= Pediculoididae). *Pyemotes* (= *Pediculoides*) *ven-tricosus* (Newport) is a widely distributed predaceous mite which attack[s] the larvae of a number of insects However, it also attacks man, produc[ing] a vesiculopapular dermatitis known as straw itch The nongrav[id] female is tiny and elongate but in the pregnant female the abdom[en] becomes enormously distended and globoid The species is ovoviviparo[us] The eggs hatch, the young mites develop to maturity, and the ne[wly] adult females are often fertilized within the body of the mother be[fore] escaping to the outside Numerous epidemics of dermatitis are attrib[uted] to infestation with this mite Farmers potters packers and broom[...] strawboard factory workers who handle wheat barley or straw are [...] parasitized by these mites Persons sleeping on straw mattresses a[re] often affected Mite laden dust from harvesting machines may be [...] considerable distances and cause infestation of inhabitants of [...]





XI 4 Photomicrographs of *Allodermanyssus sanguineus* [...] (left 108 ×) and nymph (150 × with 2 do[...] [...]ia) (Courtesy Rocky Mountain[...]

dwellings The resulting dermatitis sometimes covering the entire body has been confused with chickenpox smallpox and scabies A relatively high fever is not uncommon

For control burning of the grain stubble is recommended to destroy the mites and the insect larvae on which they feed Pyrethrins and piperonyl butoxide can be used on straw with good results Impregnation of clothing with acaricides gives effective protection against mites that cause grain itch (p 776)

Acaridae (= Tyroglyphidae) This is a cosmopolitan family of tiny mites that infest a wide variety of materials such as cereals grains and other stored products In one stage (hypopial) they may attach themselves to living insects which then serve as disseminators The dermatitis resulting from infestations with these mites is similar to that produced by the straw itch mite *Pycmotes ventricosus* Several species [illegible] *nii* (Hirst) is [illegible] vanillism (in [illegible] rom both the urinary and intestinal tracts *Tyroglyphus longior* (Gervais) may be ingested especially in cheese and may be found subsequently in the feces It is not known however to produce a true intestinal infestation The characteristic pungent flavor of Altenburger Milbenkase is due to mites Contact with the excrement or powdered bodies of these mites may readily result in allergic phenomena *Glycyphagus domesticus* (De Geer) in the closely related family GLYCYPHAGIDAE causes the well known grocers itch

Demodicidae *Demodex folliculorum* (Simon) the follicular or face mite is a microscopic vermiform parasite The adults have a transversely striated abdomen and four pairs of stubby legs (Fig XI 5) They may be found in large numbers lying head" down in hair follicles and sebaceous glands (Figs XI 6 XI 7) The usual sites of the parasite include the face nose lips forehead and the main collecting ducts of the nipples of the breast This mite has been reported in about 13 per cent of skin biopsies and is present in a large proportion of humans *Demodex folliculorum* usually produces no visible manifestations but on occasion may lead to formation of comedones ingrown hairs and dilated hair follicles Also their presence may result in the development of a slightly raised firm nodule in the skin occasionally erythematous and scaly which may enlarge slowly over a long period Application of an ointment containing the gamma isomer of benzene hexachloride (Kwell) is of therapeutic value Closely related species of *Demodex* cause mange in dogs and other animals

Trombiculidae Chiggers (red bugs harvest mites bete rouge) are the parasitic larval mites of the family TROMBICULIDAE that infest vertebrates In some areas the term chigger probably a corruption of chigoe is also applied to the burrowing flea The larvae are almost microscopic in size The adults seldom exceed 1 mm in length and are often brilliantly colored The nymphs and adults are predators living upon small arthropods and their eggs In the laboratory mosquito eggs and springtails seem to be the preferred food of certain species The

family is cosmopolitan in distribution ranging from Alaska and Labrador to New Zealand and from sea level to over 16 000 feet in the Andes Eggs which are deposited on the ground in light soil give rise to hexapod larvae which attach to their hosts including man by hooked mouth parts but they do not burrow into the skin After a prolonged period of feeding the engorged larvae fall to the ground and molt In the nymphal and adult stages they are predaceous In the northern United States there are only one or possibly two generations a year but in F[illegible]

rmatitis At t[illegible] capillaries producing bluish or purplish ecchymoses visible for months Loss of sleep and secondary infections due to scratching result in a reduced efficiency of troops or other organizations in the field *Eutrombicula alfreddugesi* (Oudemans) is the common chigger of the United States and is especially prevalent in the southern states during summer and fall (Fig XI 8) *E splendens* (Ewing) is a common troublesome species in some southeastern localities

A rickettsial disease commonly known as scrub typhus tsutsugamushi disease or flood fever occurs in Japan Formosa Australia Sumatra Malaya India Vietnam Java Philippine Islands Burma New Guinea [illegible] by the larval trom[illegible] are found in the [illegible]lents Man picks up the disease from the mites when an infected trombiculid accidentally



Figure XI 5 Photomicrograph of *Demodex folliculorum* adult showing vermiform shape and four of the eight molelike legs (phase contrast microscopy)

Figure XI 6 Longitudinal section of several mites surrounded by keratin in a hair follicle The anterior portion of the mites is directed toward the base of the follicle

Figure XI 7 Longitudinal section of *D folliculorum* in a sebaceous gland

(All three courtesy of The Louisiana State University School of Medicine)

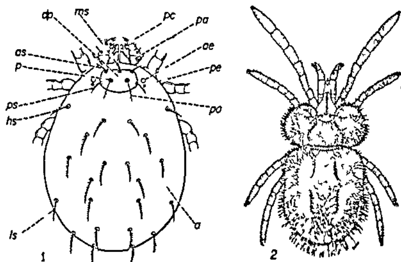


Figure XI 8 *Eutrombicula alfreddugèsi* (Oudemans) 1 Larva (North American chigger) greatly enlarged *a* abdomen *ae* anterior eye *as* anterolateral seta *dp* dorsal plate *hs* humeral seta *ls* lateral seta 1 *ms* median seta *p* pseudostigma *pa* palpus *pc* palpal claw *pe* posterior eye *po* pseudostigmatic organ *ps* posterolateral seta 2 Adult (Modified from Ewing)

gets on him and feeds The disease is transmitted only by the parasitic larva, and the rickettsiae survive through the nonparasitic nymphal and adult states to be passed through the egg to the next generation

Most areas where scrub typhus is a problem are characterized by abundant food for rodents like that supplied by abandoned gardens plantations, primary jungle, and marginal agricultural lands subjected to floods or seasonal activity such as harvesting of natural products Fringe habitats" surrounding grassy areas are dangerous locations

Trombicula (Leptotrombidium) akamushi (Brumpt), *T* (*L*) *deliensis* (Walch), *T* (*L*) *pallida* (Nagayo et al), *T* (*L*) *intermedia* (Nagayo et al), and *T* (*L*) *scutellaris* (Nagayo et al) have been reported as carriers of the scrub typhus rickettsiae (see page 94) Mites are suspected on epidemiologic grounds of being involved in the transmission of epidemic hemorrhagic fever (see page 597)

See Table XI 10 page 776 for area control of mites and for use of miticides to prevent attachment by chiggers

Sarcoptidae. Members of this family of itch mites produce skin diseases in many species of birds and mammals Members of the genus *Sarcoptes* are burrowing mites and may infest man (*Sarcoptes scabiei* var *scabiei* De Geer), sheep (*Sarcoptes scabiei* var *ovis* Mégnin), pig (*Sarcoptes scabiei* var *suis* Gerlach), goat (*Sarcoptes scabiei* var *caprae* Furstenberg), and other animals

Scabies Scabies is an irritation of the skin of man and other mammals caused by *Sarcoptes scabiei* In man it is also called itch seven year itch, Norwegian itch, sarcoptic acariasis, gale (French) Species or varieties of this mite specifically infest the epidermis of man and several

domestic animals It is probable that slight physiologic variations in the host parasite relationship operate to prevent the survival of ectopic varieties of S *scabiei* in foreign hosts for example the cat variety does not successfully establish itself in man Human scabies therefore is produced almost exclusively by the human variety of this ectoparasite Scabies in other mammals is referred to as sarcoptic mange

The distribution of this mite is coincident with the distribution of man Clinical scabies may be common among crowded populations with low standards of sanitation it occurs sporadically under a wide range of environmental conditions

Transmission of the mites occurs most readily through close bodily contact Cohabiting or sleeping with an infected person is the commonest means of acquiring the disease Owing to the frequency of interdigital lesions shaking hands is also a ready method of transfer this is especially true in the case of children who play games requiring the pro

newly impregnated female others name the larva or the nymph

The pathologic responses to the presence of scabies mites are those characteristic of previous sensitization Waste products or other substances liberated into the epidermis by the parasites promote erythema and edema The regional tissues become waterlogged and eosinophils tend to infiltrate the lesion Vesiculation eventually occurs Following rupture of the vesicle secondary infection is the rule Since the burrows are in most instances very superficial in the stratum corneum healing of the lesions occurs without scar formation (Fig XI 9) Some patients exhibit a mild eosinophilia during acute stages of the infection

The cardinal symptom of scabies is severe itching This is most intense shortly after the patient has gone to bed the gradual warming of the body inducing greater activity among the mites Loss of sleep resulting from scabies has at times been a cause of many lost man days during military operations In sensitive individuals a follicular eruption may occur

Scratching serves to kill some of the parasites and to inoculate others into new sites It also often results in the development of secondary infection

An untreated case of scabies usually terminates spontaneously after several months This seems to be due to the development of sufficient sensitization to interfere with the processes of reinoculation each new colonist being at once surrounded by transudates which interfere with its normal activity Some cases however progress into a chronic state in which the actual number of parasites is much smaller than was true in the acute stage of the disease These cases constitute the reservoir of infection Norwegian itch or crusted itch is a severe form of the disease accompanied by hyperkeratosis

Definitive diagnosis of scabies is based on demonstration of the parasite This however may be difficult to accomplish in many cases In



Figure XI 9 Adult *Sarcoptes scabiei* in burrow in epidermis

attempting to do so the physician should first study the lesions minutely with a hand lens A typical burrow is a tortuous channel a few millimeters in length appearing as a fine line on the patient s skin Its orifice may be marked by a black plug of crusted serum and mite feces Toward the blind extremity the skin is erythematous and frequently a small vesicle is found even closer to the inner end of the tunnel The adult *female mite is situated at the end of the burrow itself This region should* be incised with a fine pointed scalpel or sharp needle and the contents placed on a glass slide Ten per cent potassium hydroxide solution may be added to clear the cutaneous scales and other debris that may be present After adding a coverslip the operator should examine the preparation with a strong lens or low power microscope The finding of a mite in any stage of the life cycle is diagnostic Eggs of the mite may be observed in some cases

Lacking success in demonstrating the parasite one may make a dermatologic diagnosis in adult patients if the characteristic distribution of the lesions is observed The classic sites are the interdigital spaces wrists extensor aspects of elbows axillae (particularly the axillary folds) abdomen and belt line (especially the umbilical region) scrotum penis and areolae of the nipples In severe cases lesions may extend around the trunk to the small of the back The upper back as well as the face ever in infants (Fig XI 10) ince the occur rence of the primary lesion between the fingers is suggestive of scabies Furthermore a history of close contact with persons having characteristic symptoms especially members of the family group may be highly significant



Figure XI 10 Scabies—showing advanced lesions and characteristic distribution

Although several other dermatologic conditions may superficially resemble scabies in general it is safe to rely on the characteristic distribution of scabies lesions This distribution is mimicked only rarely by other diseases (See Table XI 10 page 776 for treatment)

Acaraphobia Delusion of dermal parasitosis by mites is referred to as acaraphobia It is of serious psychiatric implication Unsuccessful attempts to remove imaginary parasites may lead to much mutilation and excoriation Sometimes the condition may be manifested by folie a deux a psychosis shared by two persons

73

The Class Insecta (Hexapoda)

Revised by Carroll N Smith

Introduction

This the largest and most important class of arthropods both medically and otherwise is characterized by the division of the body into

three distinct portions a head composed of six (possibly seven) fused segments a thorax of three segments usually well marked and an abdomen of 11 segments of which only five to eight are usually visible The head bears the mouth parts a single pair of antennae and the eyes when present Adult insects display three pairs of legs borne ventrally by the three thoracic segments The majority of insects have wings borne dorsally on the last two thoracic segments Caudal appendages, called *cerci* are often present on the last abdominal segment

Insects are found under a wide variety of environmental conditions but only those which live as parasites in some stage of their existence or which have intimate contact with the human body or with human food are ordinarily concerned with problems of health and disease

Some 33 orders of insects are recognized at the present time Of these only 12 may be listed as of medical interest and some of these are important only in a very limited way In the list which follows the four most important orders are marked with an asterisk The medical importance of each group will be briefly summarized in this chapter and methods of control will be discussed in Chapter 77

The order of presentation is in general from the simple to the complex the COLLEMBOLA for instance being much more primitive both in structure and life history than the DIPTERA HYMENOPTERA and other highly evolved groups

List of Medically Important Orders

1 COLLEMBOLA (Springtails)
2 ORTHOPTERA (Cockroaches and others)
3 EPHEMERIDA (Mayflies)
4 TRICHOPTERA (Caddis flies)
5 MALLOPHAGA (Bird lice)
*6 ANOPLURA (Sucking lice)
*7 HEMIPTERA (Bugs)
8 COLEOPTERA (Beetles)
9 LEPIDOPTERA (Butterflies Moths)
*10 DIPTERA (Flies)
*11 SIPHONAPTERA (Fleas)
12 HYMENOPTERA (Ants Bees Wasps)

* These orders are of outstanding medical importance

Order Collembola

The Collembola are primarily phytophagous and are not usually thought of as medically important insects Two Australian species however *Entomobrya multifasciata* Tullb and *E tenuicauda* Schott have been recorded as attacking man the patients complaining of a sharp biting sensation followed by irritation and papules similar to mosquito bites with pruritus These forms derive their common name from the fact that they possess a forked muscular appendage at the posterior end of the abdomen which is used in springing into the air (Fig XI 1)

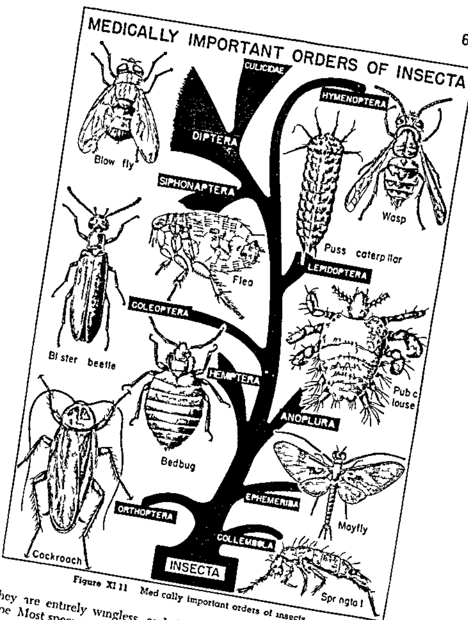


Figure XI 11 Med cally important orders of insects

hey are entirely wingless and their mouth parts are of the chewing pe Most species are less than an eighth of an inch long

Of the ORTHOPTERA, only the roaches (Family BLATTIDAE) are believed to be concerned in the transmission of disease They are cosmopolitan in distribution These insects frequent filthy places and are known to feed on both excrement and sputum if the opportunity is present Soon after they may be found on human food where both by their feces and by regurgitation they discharge some of their flora Cockroaches have been associated experimentally with a variety of bacteria including species of *Streptococcus* *Salmonella* and *Vibrio* several viruses including polio myelitis virus and protozoa There is also evidence to indicate that roaches may serve as intermediate hosts of certain helminths

Roach [illegible] antenna
and sem [illegible]
XI 11) [illegible]
directed backward Mouth parts are of the chewing type Not all species enter buildings The adults of the five types most commonly encountered in houses in the United States may be differentiated as shown in Table XI 4

Table XI 4 Key to Domestic Cockroaches in U S A

1	(6)	[illegible]	[illegible]
2	(5)	[illegible] ment	3
3	(4)	[illegible] al half	
4	(3)	[illegible] erican	
5	(2)	Wings vestigial in female in male usually reaching within four segments of tip of abdomen general color black or very dark brown Sluggish species prefers very damp environment—*Blatta orientalis* (L.) (Oriental cockroach)	
6	(1)	Smaller species (less than ¾ inch in length)	7
7	(8)	Thorax bearing two dark longitudinal dorsal stripes Wings uniform in [illegible]	
8	(7)	Th [illegible]	

Life History Cockroach eggs are deposited in a leathery capsule which may often be seen protruding from the body of the female who sometimes carries it for days Eventually she either glues the capsule to some object or merely drops it The 20 or 30 eggs (*Blattella*) hatch into tiny nymphs which closely resemble the adults except that they have no wings A gradual metamorphosis ensues Roaches are nocturnal hiding

Orthoptera of the family PHASMIDAE (walking sticks) have been known to discharge an irritating fluid which in the case of *Anisomorpha buprestoides* (Stoll) is capable of being squirted a distance of some two feet If introduced into the eye it causes excruciating pain

Order Ephemerida

The EPHEMERIDA commonly known as lake flies shad flies or may flies are of medical interest only because of their relation to certain allergic conditions For example *Hexagenia bilineata* a common species along the shores of Lake Erie occurs in such numbers in midsummer that cast skins (exuviae) are everywhere present on buildings, trees and shrubbery Persons breathing fragments of these exuviae may become highly sensitized and severe asthmatic paroxysms have been recorded (Table XI 2) There is some evidence that an extract made from the dried insects may be useful in desensitization (Fig XI 11)

Order Trichoptera

TRICHOPTERA or caddis flies are likewise causative agents of allergic symptoms at times These are mothlike creatures The hairs and scales from their bodies cause the allergic reactions

Order Mallophaga

MALLOPHAGA or biting lice are mentioned here merely to distinguish em from the sucking lice discussed below MALLOPHAGA abound chiefly birds although many species are adapted to mammalian hosts They e chewing mouth parts and feed chiefly on dandruff scurf or dried od They are exceedingly irritating when abundant and constitute a siderable problem for the veterinarian Poultry handlers are fre ntly annoyed by them but the irritation is of short duration since species will not remain on human hosts

ie biting dog louse *Trichodectes canis* is an intermediate host of the apeworm *Dipylidium caninum* a species occasionally found in man

The ANOPLURA or sucking lice are of great medical importance Apart from their significance as vectors of typhus fever trench fever and relapsing fever, their presence causes the condition known as *pediculosis* which *in sensitized individuals may be very severe*

The group numbers approximately 200 species distributed over four families Only the Family PEDICULIDAE however, contains parasites of man All human lice are *small flattened ectoparasites characterized* by a toughened skin and the complete absence of wings The mouth parts which are retractile are for piercing and sucking The head is narrow and pointed in front The eyes are either degenerate or absent The thoracic segments are fused but the thoracic region is well marked by the three pairs of jointed legs The tarsi are of one segment with a single terminal claw which together with a process of the tibia (tibial thumb) makes an effective grasping organ enabling the insect to cling to hairs or fabric Females are notched at the posterior extremity the males are rounded

Two species of hu

recognized The pub

in the pubic region

body (Fig XI 11) The head louse *Pediculus humanus capitis* (De Geer) is found on the scalp the body louse *Pediculus humanus humanus* (Linn) is found in the clothing over all parts of the body (Fig XI 12)

Human lice occur from the arctic to the tropics wherever the habits of man are such as to encourage their existence

Life History of the Body Louse (and Other Lice) The body louse *is a small flattened insect living permanently* on the person or in the clothing of man Body lice feed frequently at all stages of their existence and die within relatively few days when removed from their hosts The optimum temperature for the body louse is around 87° F They will leave a dead body a patient with fever or an individual heated by exercise

In their development lice show gradual metamorphosis Eggs (nits) are glued to hairs or fibers by the ovipositing females and when the young push aside the opercula seven to ten days later they emerge as miniature replicas of their parents They must feed within 24 hours in order to survive Growth is rapid a succession of three molts brings them to maturity in about two weeks under *favorable conditions Following* fertilization the females lay several eggs daily for most of the remainder of their short lives The entire cycle from egg to egg thus requires *only a month or slightly less The female lives* an additional 20 or 30 days during which time she may deposit from 275 to 300 eggs

Body lice hide themselves in the seams of clothing especially those of underwear and of heavier outer garments at points of pressure *Usually* they cling to the clothing even while feeding thus they may sometimes be entirely absent from the body of even a heavily infested person Nits as well as lice are found in the seams Therefore it is much more im

portant to inspect the clothing of a suspected carrier than to examine the individual himself

The increase of body lice is facilitated by infrequent laundering of clothing and their spread is favored by close crowding of individuals especially in sleeping quarters Lice may be transferred indirectly from one person to another at night when clothes are placed on hooks in open rows instead of in separate lockers

The head louse *P humanus capitis* is very similar to the body louse differing more in habits than in structure from its close relative Head lice may be induced to live in clothing and to interbreed with body lice but when undisturbed they confine themselves to hairs of the scalp They are probably of minor importance in the transmission of louse borne diseases and should be regarded principally as nuisances indicative of poor hygienic standards

Pubic lice *Phthirus pubis* inhabit hairs of the genital region less often the eyelashes moustache axillae and body surface (hairy individuals) They are usually acquired by sexual contact or from toilet seats They differ markedly from body and head lice being smaller and much less slender Their short stocky bodies and powerful grasping legs give them their vernacular name crab lice The life cycle of *P pubis* is essentially similar to that of other lice but they are less prolific a normal female laying not more than 30 eggs In addition to its predilection for the genital hairs this species is distinguished by its tendency to remain immobile for days at a time its proboscis inserted constantly in the skin It apparently prefers white to colored skin Pubic lice do not transmit louse borne diseases





♂ ♀

• XI 12 *Pediculus humanus humanus* male and female (Courtesy National Institutes of Health, U S Public Health Service)

Pediculosis The bites of lice often cause intense discomfort not only when the insect is feeding but also during the hours which follow In the case of sensitized persons symptoms may persist for many days Typically a small reddish papule appears at the site of each feeding puncture In
"weeping d
ing and eryt
restricted area Healing is usually accompanied by induration and mild fissuring of the skin with the deposition of a bronze pigment which persists indefinitely

It has been shown that repeated exposures are necessary for the development of dermal hypersensitivity and that the feces of the louse are involved in this reaction The pruritus is part of the syndrome of hypersensitivity As for the bite itself the reaction appears to involve two components a purpuric reaction which depends on the act of feeding and an inflammatory reaction dependent on sensitization If one remains lousy over an extended period the bronze pigmented condition of the skin known as "vagabonds disease" results Systemic symptoms have been recorded including general malaise mental depression and a rash somewhat like that of German measles

Untreated pediculosis of the scalp results in a condition in which the hair becomes matted together by exudate from the pustular lesions and the entire mass develops a fetid odor The severity of the condition is *often aggravated by the presence of mycotic infections* certain of which may be transmitted by the louse

At times peculiar bluish or slate colored macules which do not itch or disappear on pressure occur in association with *Phthirus pubis* These macules are about 5 cm in diameter and are located chiefly on the sides of the trunk and on the inner aspects of the thighs

Lice as Vectors of Disease Epidemic typhus trench fever and louse borne relapsing fever have each been treated at length in earlier pages of this work In the case of typhus infection is transmitted chiefly by the feces of the louse upon the skin or by air borne rickettsiae of fecal origin The bite of the louse is of doubtful importance but crushing of the louse upon the body particularly if the skin is broken (as by scratching) is a common means of transmission

With trench fever (Wolhynia fever) transmission takes places through contamination with louse feces and probably also by the bite It is of interest to note that trench fever in World War I was second only to scabies as a cause of absence from duty

The spirochetes of relapsing fever normally leave the alimentary tract of the louse and multiply in its body cavity They are transmitted to man only when the louse is crushed and rubbed into the skin

The human body louse is susceptible to experimental infection *with Pasteurella tularensis* Lice infected as first instar nymphs are capable of retaining the infection through the ensuing three molts to the adult stage It may be a potential vector of tularaemia Various species of rodent lice have been shown to transmit tularemia from host to host experimentally

Order Hemiptera* (True Bugs)

The members of this order may be winged or wingless. The species possess four wings, the first pair being thickened at the with membranous extremities overlapping at the tip. The mouth pa for piercing and sucking, the rather conspicuous beak (proboscis) arises from the front of the head is segmented and lies against the ve surface of the thorax when not in use. (In the closely related Homopt the beak arises from the posteroventral portion of the head.) The m morphosis is gradual.

This is a large order containing some 30,000 described species. T great majority are feeders on plant juices, but at least two families are considerable medical importance. The Cimicidae, or bedbugs, are a gre nuisance and constitute a control problem in hotels, dormitories, barracks, hospitals, and many private homes; the family Reduviidae (giant bed bugs, kissing bugs) include several species capable of transmitting South American trypanosomiasis (Chagas' disease). Members of at least seven other families occasionally inflict painful bites.

Family Cimicidae (Bedbugs)

Life History and Feeding Habits, Including Effect of Bites. Bed bugs inhabit houses, barracks, and other abodes, secreting themselves in crevices of walls, floors, and furniture. They are flattened insects with an oval contour and a reddish color. Despite their ungainly appearance they can run at fair speed.

Adult bedbugs are about a quarter of an inch in length. They are wingless in all stages. Their piercing and sucking segmented proboscis when not in use is carried flexed upon the ventral surface of the head and thorax.

Bedbugs feed on man only periodically, usually at night. Engorgement seldom requires more than ten to 15 minutes. After their meal the insects return to their hiding places. Lesions produced by bedbug bites are usually firm conical papules. If sensitivity is marked, large hemorrhagic bullae may form. The grouping of lesions in pairs or triplicates fairly close together and often linear in distribution is a characteristic feature. The bites may become erythematous and swollen and are sometimes characterized by severe and prolonged itching. Scratching ma result in secondary infection. These insects have been experimentally in criminated as carriers of human disease, but there is no direct evidence hat either their biting or their feces transmits infection from man to an under natural conditions. It may be pointed out that bedbugs rarely ass feces while feeding.

Fertilized female bedbugs deposit their operculated eggs singly, gluing m to solid supports in the crannies which harbor the insects by day. ingle female may deposit over 500 eggs in batches of ten to 60 over a

* The Order Hemiptera is sometimes used to include also the Homoptera (plant icadas, and other plant feeders). When such a classification is adopted, the re referred to the Suborder Heteroptera.

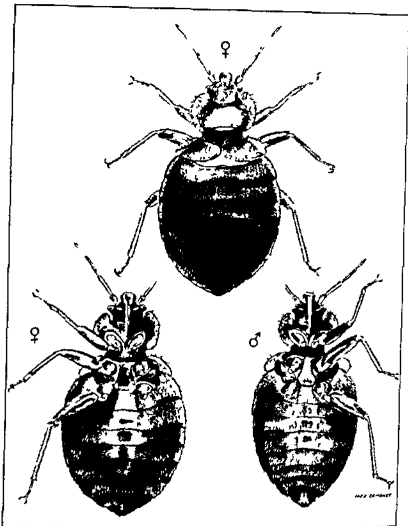


Figure XI 13 Bedbug *Cimex lectularius* (Courtesy National Institutes of Health, U S Public Health Service)

period of several months The average is probably near 200 The eggs require about a week for development, longer if the temperature is low Newly hatched bedbugs resemble adults in miniature and are known as nymphs In case human hosts are not available, bedbugs will readily feed on other mammals The normal life span is from six to eight months

Two common species of bedbug infest man *Cimex lectularius* (Linn) in most temperate regions and *C hemipterus* (Fabr) in the tropics, especially Asia These species are almost identical in appearance Closely related forms attend other warm blooded vertebrates, such as bats, but these very rarely attack man Bat bedbugs *Cimex pilosellus* (Horvath) are easy to recognize by reason of the abundant hair on the body In New Guinea man is attacked by still another species *Leptocimex boueti*

(Brumpt) whose long antennae and long legs (especially the last pair distinguish it from related forms (Figs XI 11 XI 13)

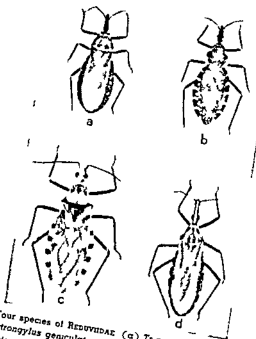
Family Reduviidae (Kissing Bugs)

Life History and Feeding Habits—Relation to Chagas Disease

This family includes well over 3000 species rather widely distributed The majority feed on the blood of insects a habit which has given them the name assassin bugs At least 75 however feed on the blood of mammals including man Certain of these are responsible for the transmission in South and Central America of *Trypanosoma cruzi* the causative agent of Chagas disease Several species of bugs may serve as vectors notably *Panstrongylus megistus* Pinto The opossum and armadillo are favorite hosts of this species The bloodsucking reduviids are sometimes treated as a separate family the Triatomidae (Fig XI 14)

Panstrongylus megistus This species is large averaging 30 mm in length and may be recognized by the bright red spots on the thorax at the base of the wings and on the lateral margins of the abdominal segments

Both adults and nymphs hide during the day in cracks or crevices in the walls of houses or in other sites emerging at night to seek their



…ure XI.14 Four species of REDUVIIDAE (a) *Triatoma protracta* (b) *Triatoma san…ga* (c) *Panstrongylus geniculatus* (d) *Mestor pallescens* (Herms Medical Ento…y by permission of The Macmillan Company)

blood meal In attacking human hosts they bite the cheeks near the eye by preference hence the common name, 'barbeiros' Less commonly the angle of the mouth is the site of attack The trypanosomes which are passed in the bug's feces may enter the puncture wound after the bug has fed, but the bite itself is probably not infective

The females deposit their eggs, which are about 2 mm long in various hiding places where they undergo incubation for approximately 20 days Each female lays close to 200 eggs The nymphs, which molt five times develop over a period of nearly a year, and the adults live for a year or more after attaining maturity

Symptoms of the Bite. In the case of *P. megistus* the bite is relatively painless and the symptoms are negligible, unless secondary infection occurs Considerable edema about the eye (Romaña's sign) is usually associated with the early stages of Chagas' disease but this is due to the reaction to the parasite and not to the bite of the insect Certain other reduviids however, especially *Reduvius personatus* Linn, have been known to cause nausea, palpitation and generalized urticaria by their bites

Other Vectors and Potential Vectors. The first of the accompanying tables (Table XI 5) lists various species believed to be capable of transmitting Chagas' disease in the areas where that disease exists (Mexico, Central and South America) It should be mentioned that *Triatoma infestans* Klug has recently gained considerable prominence as a vector in those countries where it occurs Table XI 6 tabulates those species which have been found r [illegible] within the boundaries of the U [illegible] United States generally [illegible] tions for potential vectors of *T cruzi* This and other factors which limit human contact with reduviid bugs probably are important reasons that Chagas' disease is rare in the United States

Table XI.5. Reduviid Bugs Reported as Vectors of *Trypanosoma cruzi* in Mexico, Central and South America

LOCATION	SPECIES OF BUG
Mexico	*Triatoma sanguisuga* LeConte, *Rhodnius prolixus* Stal *T hegneri*
Guatemala	*Triatoma dimidiata* Latr
Panama	*Eratyrus cuspidatus* Stal *Rhodnius pallescens* Barber, *R prolixus* Stal, *Panstrongylus geniculatus* Latr, *Triatoma dimidiata* Latr
Argentina	[illegible] *Triatoma infestans* Klug
Bolivia	[illegible]
Brazil	[illegible] Neiva *Eutriatoma sordida* [illegible] don a [illegible]ticeps Stal
Chile	*Mepraia spinolai* Porter, *Triatoma infestans* Klug
Colombia	*Rhodnius prolixus* Stal *R pictipes* Stal
Paraguay	*Eutria sordida* Pinto
Uruguay	*Eutriatoma sordida* Pinto, *Triatoma infestans* Klug
Venezuela	*Eratyrus cuspidatus* Stal *Eutriatoma nigromaculatus* Stal, *Panstrongylus rufotuberculatus* Champ, *Psammolestes arthuri* Pinto *Psammolestes geniculatus* Latr, *Rhodnius prolixus* Stal
Ecuador	*Triatoma dimidiata*

Table XI.6. Reduviid Bugs Naturally Infected with *Trypanosoma cruzi* (U S A)

SPECIES	GEOGRAPHIC LOCATION	HOST ANIMALS OR HIDING PLACES
Triatoma protracta Uhler	New Mexico California	*Neotoma* (wood rats)
Triatoma uhleri Neiva	Arizona California	*Neotoma*
Triatoma gerstakeri Stal	Texas	*Neotoma*
Triatoma heidmanni Neiva	Texas	Dwellings—bedding
Triatoma longipes Barber	Arizona	Sleeping bags
Triatoma protracta woodi Usinger	New Mexico	*Neotoma*
Triatoma ambigua Neiva	Texas	*Neotoma*
Triatoma sanguisuga LeConte	Texas	*Neotoma*

Order Coleoptera (Beetles)

Typical beetles have two pairs of wings, the first of which is modified to function as wing covers and is called *elytra* In most species the elytra are hard and horny and meet in a straight line down the back, but certain medically important species are exceptional in this respect The second pair of wings, which is folded beneath the elytra when not in use, is usually membranous in character and when expanded constitutes an effective organ of flight The mouth parts are adapted for chewing The

portant from a medical point of view than certain other orders (DIPTERA, ANOPLURA), COLEOPTERA affect the health of man in at least four different ways (1) by vesicating and poisonous effects, (2) as parasitic larvae (canthariasis), (3) as hosts of helminthic parasites, (4) by mechanical transmission of infective organisms

Vesicating and Poisonous Effects

Beetles of the Family MELOIDAE contain in their body fluids a cryptotoxic principle which if rubbed upon the skin, has marked blistering effects In Europe the best known of the blister beetles is *Cantharis vesicatoria*, the Spanish fly *Epicaut*
most common species in the eas
nates in the southwestern part
tles causes a very slight tingling and burning sensation within about ten minutes In two or three hours, the vesicle or bulla appears as a flat-topped collection of fluid The bulla arises from a noninflammatory base in about eight to ten hours and typically is asymptomatic The bullae are usually linear in arrangement, often only one long vesicle is present, al

though sometimes multiple vesicles coalesce to form a single linear lesion Workers in potato fields where large numbers of beetles are feeding may show multiple lesions on exposed surfaces Accidental crushing of the beetles in the field may lead to a vesicular dermatitis, and the victim will not know how the condition was acquired The absence of a central puncture wound, however, will usually enable the physician to differentiate between this condition and an ordinary insect bite Children going barefoot or persons under or near white outdoor lights may be affected Gentle pressure on the top of the beetle causes the vesicating fluid to exude from the knee joints prothorax and genitalia of the insect Thus when a person brushes off the insect, a stimulus is provided for secretion of cantharidin (Fig XI 11)

The dermatosis is seasonal in the United States, occurring most commonly in July, August and September Treatment depends upon the location of the lesions Bullae on an area unlikely to be traumatized resolve in a few days, and the overlying epidermis flakes off within a week Protection of the affected area is adequate treatment Larger bullae may be drained and then protected with an occlusive dressing using an antibiotic ointment There is no drug known which acts specifically to counteract the vesicating effect

The urticating principle, cantharidin has long been used in medicine as a blistering agent Topical application of cantharidin may destroy pen [illegible] ut it is not recommended for mosaic [illegible] an aphrodisiac under the name of [illegible] ffect may result, if any, reportedly requires a dosage which may produce renal damage

Another family, the Staphylinidae (rove beetles), also contains forms with vesicating properties Medically important forms occur in the Orient in Java in tropical South and East Africa and South America The irritating substance which they produce is *not* cantharidin, though somewhat similar in its pharmacologic effect A peculiarity of staphylinid poison is that the blistering does not occur until a day or two after contact

A blistering effect has been reported from southeast Africa as a result of contact with a night flying beetle of the family Paussidae, which secretes a highly acid liquid substance Also in certain islands of the Pacific, at least two species of *Sessinia* (coconut beetles) of the Family Oedemeridae are reputed to cause burning pain at the point of contact followed by a large but relatively harmless blister

A quite different example of urtication is found in the small flour beetle, *Tribolium confusum*, which gives off a gaseous substance irritating to the eyes and nasal membranes

Canthariasis

Infection of man by beetles at any stage of their life cycle is known as canthariasis Intestinal urinary, ocular, nasal aural and cutaneous varieties have been recorded The condition is rare as it follows the accidental entrance of eggs, larvae or adults into the human body An intense diarrhea among children in Ceylon is believed to be due to intestinal canthariasis

Beetles as Hosts to Helminthic Parasites

Various species belonging to different families are known to harbor cysticercoids of the rat and mouse tapeworms, *Hymenolepis diminuta* and *H nana* Other species serve as intermediate hosts of various ACANTHO CEPHALA and nematodes

Mechanical Transmission of Microorganisms by Beetles

Adults of STAPHYLINIDAE (rove beetles), SILPHIDAE (carrion beetles) and HISTERIDAE all feed upon dead animal matter of one form or another They may thus convey infection (1) upon their bodies, legs or mouth parts or (2) by way of the alimentary tract Species of DERMESTIDAE feed on such material chiefly in the larval stage Anthrax bacilli have been found in the feces of *Dermestes vulpinus* F which had developed

copro

cted to

human feces Certain species of "tumble bugs" form balls of feces and roll them away for burial (food storage) at a distance, other dung beetles bury feces directly and produce mounds of disturbed soil at the site of deposition The larger coprophagous species excrete considerable amounts of fecal material during their feeding and burrowing activities This, as well as transport of mammalian feces to a distance, may be a factor in the dissemination of microorganisms present in human and ani mal stools Stools may be buried by numbers of dung beetles within a few hours after deposition The rapid removal of stools by these beetles may have indirect influence on the degree of pollution and worm infesta tion of soil by maintaining defecation sites in acceptable condition for repeated use and thus enhancing the infection potential of particular spots Hookworm and *Ascaris* eggs ingested by dung beetles usually are destroyed by mastication owing to the grinding action of the beetle's mandibles However, when soil conditions are favorable for their devel opment, hookworm larvae reach the soil wherever beetles bury infected feces The activities of the beetles thus result in lateral dispersion of hookworms in the soil Conversely beetles work against effective dis semination of *Ascaris* eggs both by destroying them through ingestion and by burying them

Order Lepidoptera

(Butterflies and Moths)

Species in this order are characterized by the presence of numerous scales (modified hairs) on the body and wings and by the nature of their mouth parts, which are in the form of a sucking tube that is coiled be

neath the head when not in use Except for a few wingless forms, two pairs of wings are present The metamorphosis is complete, Their larvae which are called caterpillars, may be either smooth and wormlike, or thickly covered with hairs, according to the species concerned Most moths pupate inside a silken covering, the cocoon spun by the larva just prior to transformation

The order is of minor significance from a medical point of view nevertheless, as with the beetles, certain important medical relationships exist

Urticating Hairs

There are several groups of caterpillars which bear hairs capable of irritating the skin and mucous membranes These may be rather simple bristles or heavy hollowed spines, but all are associated with poison secreting cells or glands Persons coming into direct contact with such caterpillars are pierced by the hairs or fragments of them with resultant urticating effects The more slender types of hair may occasionally become detached and cause annoyance when they are blown about by the wind

Symptoms of Poisoning by Caterpillar Hairs. The exact nature of caterpillar poison is unknown Browntail caterpillar venom is soluble in alkalies and may be inactivated by exposure to a temperature of 115° C Increased susceptibility rather than immunity appears to result from repeated exposure

In the United States the 'puss caterpillar" or "stinging asp" (*Megalopyge opercularis* J E Smith) is by far the most important species In certain p

occur

its abu

There is at first an intense, burning pain, which spreads rapidly beyond the site of contact, and is followed by itching The pain may last as long as 12 hours The affected area develops whitish papules which soon become red Moderate local swelling may occur, and regional lymph nodes occasionally may be enlarged There may be nausea and fever with numbness and swelling of the part affected In rare cases symptoms may be alarming Paralysis may ensue, particularly if the stings are received in the region of the neck Severe symptoms may persist for as long as six days

The hairs of the browntail moth caterpillar, *Nygma phaeorrhoca* (Don) produce a severe dermatitis but do not, as a rule, cause systemic symptoms Necrosis of epidermal cells, the formation of vesicles and perivascular inflammation in the corium constitute the characteristic pathologic processes of "browntail rash"

Windblown hairs of various species have been known to cause a painful nodular conjunctivitis (*ophthalmia nodosa*) As many as 27 nodules have been excised from the eye of a child, most of which proved on microscopic examination to contain urticating hairs

Treatment. Codeine usually is required for relief of pain from venenation by the "puss caterpillar" Usually no further treatment is neces

sary Acetylsalicylic acid does not afford relief Calcium gluconate or Benadryl administered intravenously has been employed with some success

Alkaline compresses may be used to give a measure of relief for dermatitis from the browntail moth Local application of warm ammonia water or baking soda is recommended

Scoleciasis

This is the term [illegible]
ous larvae sor[illegible]
most authentic [illegible]
larva of *Pieris* s[illegible]
[illegible] age worm) with raw cabbage [illegible] Poisoning from ingesting the [illegible] The

Lepidoptera as Hosts of Helminth Parasites

The rat tapeworm *Hymenolepis diminuta* (Rudolphi) may pass its cysticercoid stage in several species of MICROLEPIDOPTERA

Order Diptera

This is the most important order of insects from a medical point of view Malaria yellow fever dengue kala azar oriental sore espundia African sleeping sickness several types of filariasis Carrión s disease pappataci fever and certain of the viral encephalitides are transmitted by dipterous vectors In addition cholera typhoid amebiasis shigellosis and various diarrheas conjunctivitis and occasionally trachoma are distributed by the activities of flies

For an account of the medically important DIPTERA by families see Chapter 74 page 717

Order Siphonaptera (Fleas)

leas are laterally compressed highly chitinized and sclerotized small
ngless bloodsucking ectoparasites of mammals and birds The com
species vary from 1 5 to 4 mm in length
he mouth parts are adapted for piercing and sucking and the power
long legs for jumping The impregnated chigoe flea is exceptional in
it burrows into the skin and is largely sessile
he head bears in addition to mouth parts inconspicuous annulated
nnae which normally lie in grooves The eyes are simple when
nt

The thorax is divided into three segments, and the abdomen is variously stated to consist of ten to 12 Both present a series of chitinized plates, the *sclerites* The dorsal plates are known as *tergites*, the lateral as *pleurites* and the ventral as *sternites*

The *ctenidia*, or combs, bold backward pointing rows of spines, are characteristic structures, the *genal comb* being just above the mouth parts and the pronotal comb dorsally on the first thoracic segment Their presence or absence in either location or both locations is important in classification Other taxonomic characters are the shape of the head, the cranial grooves, the male terminalia the receptaculum seminis in the female, and the location and arrangement of certain bristles spinelets and spurs (Figs XI 11 XI 15)

Life History. Flea eggs are glistening white and are deposited dry among the hairs of the host or in the nest The developing embryo is provided with a sharp spine on the head by means of which the eggshell is shredded and the embryo liberated The larvae are wormlike, have 13 segments and biting mouthparts They feed chiefly on organic debris There are three larval instars At the end of the feeding period the larva spins a cocoon and pupates The length of the pupal stage is, to a considerable extent, determined by the existing temperature The time required for completion of the entire life cycle varies from about three weeks to several months

Some species may live for several months without feeding thus enabling them to act as "reservoirs" of *Pasteurella pestis* in the prolonged intervals between blood meals

There are more than 800 described species of fleas These are grouped in six or more families, of which the Pulicidae, Dolichopsyllidae and Hectopsyllidae are of special medical importance

The family Pulicidae contains *Ctenocephalides felis* (Bouche) and *C canis* (Curtis), the cat and dog fleas respectively, *Pulex irritans* Linn, the human flea, several species of *Xenopsylla*, and a ground squirrel flea, *Hoplopsyllus anomalus* Baker

Ctenocephalides felis and *C canis* are almost cosmopolitan In both species, genal and pronotal combs are present The genal comb consists of eight spines and the pronotal of 16 *Pulex irritans* has been reported from all of the major zoographic regions but is absent from some large cities and present in some sparsely populated areas *Xenopsylla cheopis* is widely disseminated in many countries It has been recorded from 19 of the United States and has become established as far north as Michigan

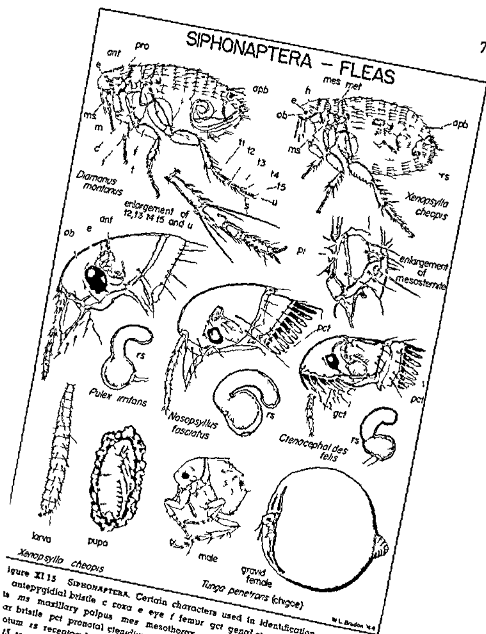
[illegible] ar in that they both

[illegible] there is one rod

[illegible] rsally and another

extending nearly perpendicularly In *P irritans* the perpendicular rod is absent In addition, the ocular bristle of *X cheopis* arises in front of and just above the middle of the eye, whereas in *P irritans* it arises near the lower anterior margin (Fig XI 15) Other important species of *Xenopsylla* are *X brasiliensis*, *X eridos*, *X nubicus*, *X piriei* and *X astia*, all of which are implicated in plague transmission

The family Dolichopsyllidae contains medically important species of



igure XI 15 SIPHONAPTERA. Certain characters used in identification *ant* antenna antepygidial bristle *c* coxa *e* eye *f* femur *gct* genal ctenidium *h* head *m* mouth ts *ms* maxillary palpus *mes* mesothorax *met*, metathorax *ms*, mesosternite *ob* ar bristle *pct* pronotal ctenidium *pi* perpendicular incrassation of mesostern te *pro* otum *rs* receptaculum seminis *s* spine at tip of second tarsus *t* trochanter *tt* tibia *t5* tarsus 1 2 3, 4 5 *u* ungues

several genera Among these are a ground squirrel flea *Diamanus montanus* Baker the temperate zone rat flea *Nosopsyllus fasciatus* (Bosc) the South American cavy flea *Rhopalopsyllus cavicola* (Weyenb) and two rodent fleas from the Russian steppes and Manchuria *Ceratophyllus tesquorum* (Wagner) and *Oropsylla silantiewi* (Wagner) respectively All are vectors of *P pestis* among rodents and *N fasciatus* is also a vector of murine typhus among rats

The family HECTOPSYLLIDAE is represented by two important genera *Echidnophaga* Olliff and *Tunga* Jarocki

Echidnophaga gallinacea (Westwood) the stick tight flea is widely distributed in tropical and subtropical regions including Australia In the United States it has been listed from 22 states and is reported as permanently established as far north as Virginia and Kansas It is a serious pest of poultry in the south and attacks many species of vertebrates including dogs cats rats and man When feeding the female attaches firmly to its host Thus rats and wild birds may function in its dispersal far beyond its normal range Although it is reported as relatively rare on rats in the United States it is said to occur in large numbers on rats in Madagascar *Pasteurella pestis* has been recovered from these fleas taken from the burrowing owl *Speotyto cunicularia* in the western states

Tunga penetrans (Linn) the burrowing flea is widely distributed in

beneath the nail or in other parts of the body where its abdomen becomes greatly distended by blood and developing eggs There is intense itching and inflammation and not uncommonly secondary infection In Central America tetanus and gas gangrene frequently occur Autoamputation of the toes has been attributed to infestation with this flea in Angola (Fig XI 16)

Surgical removal of the intact flea is recommended This consists of slightly enlarging the entrance hole of the flea by the use of a sterile needle followed by gentle pressure on the sides of the aperture The entire flea is thus forced out The wound is then cleansed and an antiseptic dressing applied On the other hand excellent results are reported from the use of an initial Lysol bath followed by puncturing each flea with a needle A second Lysol bath kills the liberated eggs and sterilizes the wound Five other species of *Tunga* are known one of which appears in Brazil and one in China

Relation to Disease Fleas serve as vectors of the rickettsiae of murine typhus from rat to rat and from rat to man They are "reservoirs" of *Pasteurella pestis* and transmit this organism from rat to rat rat to man and man to man and in sylvatic plague from wild rodent to wild rodent from wild rodent to rat and from both to man They are also intermediate hosts of several tapeworms

The bites of some fleas are extremely annoying and result in a derma

the belt line shoulders and hips where clothing fits snugly and also on the legs Severe reactions are more frequent in children Most persons initially allergic to flea bites cease to have any significant reaction to sub sequent bites within a year or two Flea bites are not seasonal in most areas Like other insect bites those of fleas are discrete and when seen early may show a small central hemorrhagic punctum The location and grouping of flea bites are important diagnostic features Desensitization by the use of flea antigen which is commercially available in the United States has been reported helpful

Although the flea fauna is to some extent characteristic for certain hosts host specificity is not marked The fleas that most frequently bite man are said to be *Ctenocephalides canis* (Curt) *Ctenocephalides felis* (Bouche) the dog and cat fleas respectively and *Pulex irritans* Linn

On the other hand *Diamanus montanus* Baker and *Hoplopsyllus anomalus* Baker are parasites of certain ground squirrels Neither is reported as a frequent parasite of man but an interchange of parasites between rats and ground squirrels is not uncommon

Bubonic plague is transmitted to man primarily by the bite of the tropical rat flea *Xenopsylla cheopis* It has been suggested that the human flea *Pulex irritans* may serve to convey the infection from person to person but the evidence is not conclusive Although many fleas feeding on an infected rat take up plague organisms only a few become effective vectors for transmitting the disease to other rodents or to man



Figure XI 16 Chigoe flea *Tunga penetrans* embedded in characteristic position below nail (Courtesy Dr T H G Aitken)

In the stomach of effective vectors the plague organisms *Pasteurella pestis* multiply somewhat as in a culture tube until they obstruct the part of the alimentary canal of the fleas known as the proventriculus This may require as long as two or three weeks When this obstruction occurs the flea encounters difficulty in obtaining another blood meal In endeavoring to do so it is likely to regurgitate plague organisms into the wound made by the piercing organs This so-called "blocked flea" remains infective during its life but this often is shortened by the very existence of the blocking Blocked fleas may live several weeks

Intensive studies in widely separated endemic areas have served to amplify rather than simplify the already complex ecology of *sylvatic plague* In the western United States about 30 species of rodents and two species of lagomorphs have been found plague infected and more than 30 species of fleas are capable of harboring *Pasteurella pestis* Of the two species of fleas most frequently found on the ground squirrel *Citellus beecheyi beecheyi* and *Diamanus montanus* the latter is by far the more efficient vector This flea has also been recovered from pack rats

squirrels The stick tight flea *Echidnophaga gallinacea* (West) with a wide variety of hosts including the burrowing owl *Speotyto cunicularia* has been found naturally infected (see Chapter 27)

On epidemiologic grounds *P irritans* was under suspicion as the vector in the Paris epidemic (1921) On similar grounds it has been indicated as a vector in the mountainous regions of Ecuador where *X cheopis does not occur In some areas in the western United States* the prairie dog (*Cynomys* spp) a natural host of this flea constitutes an important rodent reservoir

Xenopsylla cheopis is considered the most common flea vector of murine typhus (see Chapter 7)

Order Hymenoptera

This order includes the bees wasps and ants Except for certain wingless forms these insects are characterized by the presence of four membranous *wings the anterior and posterior* wings of the same side being held together by a row of fine hooks termed hamuli The mouth parts are formed for chewing or for both chewing and sucking but never for sucking blood The abdomen in the female is usually provided with a sting piercer or saw The metamorphosis *is complete* (*egg* larva pupa adult) (Fig XI 11)

Hymenoptera are of medical interest for two reasons (1) the poison

ous effects of their stings (2) as mechanical vectors of parasites (of very slight importance)

The Poisonous Effects of Stings

The sting of the female hymenopteron is really a modified ovipositor composed (in the honeybee) of a central shaft two lateral lancets or *darts* and two finger like *sting palpi* The darts are provided with sharp recurved teeth

In most species the poison glands are of two types The acid secreting gland a paired structure produces a toxin which is capable of paralyzing other insects Those species which provision their nests with living prey have only this gland

The second gland usually single produces an altogether different substance alkaline in nature Like the acid secretion this substance is only mildly irritating in itself but when the two are combined as occurs at the time of the sting typical and painful symptoms ensue In cases when the stinger remains in the wound the muscles continue to contract for some minutes thereby forcing the shaft deeper into the subcutaneous tissue and causing a great

The composition of be
stood Formic acid once
not a constituent A non nitrogenous substance related in its action to saponins an active principle of snake poisons has been isolated Histamine has been shown to be a constituent Through electrophoresis and paper chromatography it is now known that bee venom contains a number of basic and acid components of which two principal ones are basic One of these a protein termed "melittin contains the hemolytic factor and also causes general and local effects The other basic component contains the most powerful dehydrogenase inhibitor known—more powerful than that of cobra venom—and a hyaluronidase which may assist permeation of the venom Bee venom is hemolytic the factor responsible has been separated into two components a lecithinase which transforms lecithin into hemolytic lysolethicin and another which has a direct hemolytic action

Bee venom has been shown to have four characteristic toxic effects The hemolytic effect (similar to rattlesnake poisoning) resembles that of sapotoxins and explains the occasional occurrence of hemoglobinuria and melena in bee sting victims The venom also elevates the coagulation time either by preventing the formation of thrombokinase or interfering with its action A neurotoxic effect is evident from the paralysis produced by the venom in some species Finally the histamine effect produced by this component of the venom accounts for the local reaction of redness flare and wheal of the skin The venom of bees also has been shown to cause localized muscular necrosis edema and cellular infiltration at the site of the sting in unsensitized tissues

Local s oll

same time are necessary for a lethal dose of poison In certain instances however individuals become sensitized after which a single sting may produce alarming and occasionally fatal results The severity of allergic manifestations depends upon the degree of hypersensitivity Some of the manifestations in order of frequency are generalized urticaria angio edema shock with respiratory and cardiac impairment cyanosis asthma with wheezing or choking nausea vomiting chest pain and occasion ally fever and convulsions The venom poisoning may produce a leu kemoid blood picture with immature white cells in peripheral blood and leukocytosis

In fatal cases symptoms of cyanosis shock and respiratory difficulty last about 30 minutes and death results from anaphylactic shock Autopsy usually reveals laryngeal edema with obstruction by both bullous folds and mucus pulmonary emphysema acute pulmonary and cerebral edema cardiac dilatation and visceral congestion

The whole question of allergy in relation to bee venom is somewhat confused since bees frequently carry various pollens and other sub stances that they have picked up while visiting flowers and other sources of food These rather than bee venom may be responsible for the hay fever and asthmatic symptoms reported by persons handling hives bee frames or honey or in other ways having contact with bees Such facts argue for the utilization of whole bee extract rather than venom alone in desensitizing procedures

Gel diffusion studies indicate that the yellow jacket yellow hornet black hornet
each insect cc
Homologous
animals whereas heterologous antigens produce lesser degrees of shock or none The antigens vary in their ability to produce sensitization yel low jacket is the most potent sensitizer whereas black hornet antigen is the least potent Some individuals with little sensitivity to the above venenating insects may be extremely reactive to the venom of fire ants When a severe allergic reaction to an insect sting occurs and the of fending insect can be identified accurately desensitization with antigen from the appropriate species may be safe Testing for sensitivity to anti gens of other insects also may be desirable If the insect causing the severe reaction cannot be identified or if there is a possibility of sensi tivity to other stinging insects desensitization with a combined antigen including at least bee wasp yellow jacket and hornet extracts appears to be advisable Antigen of the fire ant should be employed or added if reactions to stings or sensitivity tests indicate the need

The honeybee *Apis mellifica* falls in the Family Apidae bumblebees (various species of *Bombus*) belong in the Bombidae Both however are included in the Superfamily Apoidea Unlike the honeybee and some wasps representatives of *Bombus* do not leave the stinging apparatus in the wound but may withdraw and insert the stinger repeatedly Certain South American bees are stingless but nevertheless cause great discom fort by biting and twisting with their mandibles When aroused they

tend to attack the scalp in large numbers Some inject an irritating saliva at the point of the bite

Beside the APOIDEA the following five superfamilies of HYMENOPTERA contain stinging forms

Certain of the FORMICOIDEA or true ants may possess dangerous stings fire ants harvester ants and numerous tropical species are to be avoided for this reason The VESPOIDEA include wasps hornets yellow jackets velvet ants mud daubers and mason wasps all are capable of stinging Less often encountered are thread waisted wasps of the insect destroying SPHECOIDEA The BETHYLOIDEA and ICHNEUMONOIDEA include various wasplike insects most of them of little medical concern

Treatment of Hymenopterous Stings The necessity and extent of treatment depend largely on the severity of the stinging and of the patient's reaction Although bee stings usually are just an inconsequential nuisance they may occasionally be disastrous

1 If the sting remains in the tissue as is usually the case with the worker honeybee it should be removed by scraping with a knife blade or scalpel If the protruding end of the sting is grasped with forceps or fingers the squeezing effect will inject more venom under the skin

2 Occasionally the pain is severe enough to require local medication Phenindamine (Thephorin) ointment gently massaged into the site of the sting may afford prompt relief of pain and possibly prevent swelling Rhulicream Quotane and hydrocortisone acetate (1 per cent) all in the form of ointments are useful for topical application Tincture of iodine is reportedly a beneficial remedy A mixture of equal portions of vinegar and salt rubbed into the site of the sting has been recommended Antihistaminics taken orally may be employed to ameliorate the residual reactions A large fluid intake and catharsis are useful in hastening the elimination of venom

3 Epinephrine (Adrenalin) is the drug of choice for the treatment of acute systemic reactions and preferably should be administered intravenously From 5 to 15 minims (0 3 to 1 ml) of 1 1000 epinephrine hy

casions Cortisone has proved beneficial when dangerous symptoms persisted in spite of epinephrine and antihistamine therapy Calcium gluconate given intravenously has resulted in improvement when epinephrine failed Treatment must be instituted promptly in some acute cases a delay of minutes can lead to a fatal outcome Effective drugs must be given parenterally since absorption of drugs by the oral route is usually too slow to counteract the rapid effect of the poison

4 Oxygen should be given to combat anoxia in the event that respiratory obstruction is present Tracheotomy may be necessary in cases with obstruction from laryngeal edema however difficulty may be encountered if associated with bronchiospasm and tenacious mucus Stings of the mouth may cause sufficient swelling to require tracheotomy Fluids should be given intravenously if needed to help counteract the shock

5 Persons who are hypersensitive to insect stings should carry epine

phrine and a syringe so that they may treat themselves intramuscularly in case they are stung Their families also should learn to administer epinephrine injections

As an alternative Nephenalin tablets should be carried or kept immediately available Before use the mouth should be emptied of saliva by swallowing the Nephenalin tablet is then placed under the tongue *for five minutes without* swallowing These tablets contain n isopropyl arterenol hydrochloride in the sugar coating for sublingual absorption and subsequent relief After five minutes under the tongue the coating *is dissolved and the nucleus of the tablet containing theophylline ephedrine sulfate and phenobarbital is swallowed for additional relief* Uncoated tablets of antihistamine should also be carried at all times

6 *After recovery from an acute systemic reaction desensitization with* appropriate antigenic extracts should be undertaken

Prophylaxis and Control Persons who have shown marked sen*sitivity to hymenopteran venom may be desensitized* (*see p 712*) *Nests* of ants or wasps in proximity to houses may be eliminated by spraying with a suitable insecticide such as chlordane dieldrin or heptachlor

The Fire Ant

Vincent J Derbes and Rodney C Jung

Many hymenopterans attack humans but few with the aggressive viciousness of the imported fire ant *Solenopsis saevissima richteri* These annoying and destructive pests slipped unnoticed into the United States probably as cargo stowaways from a South American port Their similarity to indigenous fire ants *S geminata* caused them to be overlooked for some years Entomologists attribute their rapid spread to flying and crawling drifting downstream in logs traveling aboard cars trucks trains and airplanes and to being transported in nursery stock Today they are scattered over at least ten southern states

Pathogenesis The *ant first fixes itself* with the mandibles pulling on the skin and pinching and raising it slightly thus causing a definite sensation of pain before the sting is inserted It then arches its back at the peduncle and inserts the stinger maintaining this position usually [illegible] and using the head [illegible] three additional sites [illegible] diagnosis A flare of [illegible] minute a wheal appears and grows [illegible] ter This persists for about one hour regardless of local therapy Small prominences may be seen at the site of stings one and one half to two hours later *Within* four hours it is evident that these elevations consist of quite superficial

vesicles containing thin clear fluid Loss of this fluid by rupture or drying produces depressed centers Eight to ten hours later the vesicular fluid is noted to be cloudy and becomes purulent soon thereafter After 24 hours the sting sites are slightly umbilicated pustules sometimes surrounded by a narrow red halo In other instances there is a large red edematous painful area Such areas are often seen clinically for multiple stings are the rule The pustule remains three to ten days it then ruptures and a crust is formed Cultures of pustules consistently give negative re

Fig XI 17

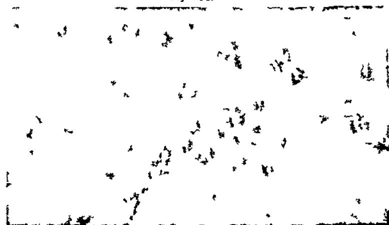




Fig XI 18

Figure XI 17 Clusters of pustules on arm at sites of fire ant stings
Figure XI.18 Section of biopsied pustule caused by fire ant sting
(Courtesy of Dr Vincent J Derbes and Dr Rodney C Jung Tulane University School of Medicine)

sults except for occasional contaminants and organisms are not seen in sections of biopsied tissue (Fig XI 18)

On the lower extremities particularly pigmented macules persist for days or weeks One may see *residual fibrotic nodules of 2 or 3 mm diameter* especially in older persons These are of the type that has been described under the designations dermatofibroma of histiocytoma cutis Frequently at the sites of ant stings particularly on the lower extremities *patients* tend to develop patches of infectious eczematoid dermatitis which may be persistent

Reactions to the stings of the fire ant are of two types local and systemic The local changes (immediate punctum wheal and flare sterile pustule) suggest strongly that a powerful necrotizing toxin of unknown nature is responsible This is known not to be formic acid because of its alkaline reaction and the intense inflammatory response to minute quantities of injecta

Systemic reactions after ant stings are febrile and allergic The fever is seldom severe 24 to 48 hour elevations of 1 or 2 degrees Fahrenheit are customary The allergic reactions are first manifested by increasing local *response to ant stings—larger and larger areas of local edema erythema* and discomfort The pustular elements do not similarly increase in size again suggesting that allergy plays no role in the production of the pustule Patients may develop generalized urticaria and bronchial asthma *shortly after being stung This reaction to the ant sting must be relatively uncommon* at least at present although it is extremely frequent after bee stings

Histopathologic examination of a 72 hour pustule discloses a thin roofed lesion containing many eosinophils leukocytes plasma cells lymphocytes and cells with small pyknotic nuclei The floor of the pustule is an edematous epidermis except at its center where the epidermal floor is completely absent and the cellular infiltrate breaks through to extend profusely into the underlying necrotic tissue Mantles of cellular infiltrate also extend laterally and more deeply about the dilated blood vessels and the nearby sweat glands (Fig XI 18)

These histopathologic changes are not like those generally seen following other insect stings or bites The inflammatory reaction is much more severe the consistent formation of a pustule is a differentiating feature and the necrosis is of a degree that often leads to scar formation

Treatment The allergic manifestations which result from stings of the fire ant may be treated in the usual way with antihistaminic drugs epinephrine and its congeners the various corticosteroid agents and ACTH The pustules are entirely refractory to these agents and to antibiotic drugs *as would be expected from the sterile nature* of these lesions Whole bee extract has been used with beneficial results to desensitize patients allergic to bees wasps and ants Extracts of the fire ant have also been employed in patients with systemic reactions following the sting of this insect *The changes produced* in the skin by the sting of the fire ant are necrotic and it is not likely that these could be prevented by desensitization

74

The Order Diptera

Luther S West

The DIPTERA or true flies are the most important single order of insects from a medical standpoint Some are external blood sucking parasites Others develop as larvae within the human host Dipterous species also serve as vectors of protozoal viral bacterial and helminthic diseases Their vectorship is sometimes mechanical sometimes cyclical sometimes cyclicopropagative The distribution of the group is worldwide but more are found in warmer regions

Characterization. The winged members of the order have only two wings borne by the mesothorax The second pair of wings is represented merely by a pair of knobbed hairs the *halteres* (see Fig XI 20) which are believed to function in the maintenance of equilibrium The mouthparts are always formed for sucking but only in comparatively few groups is there adaptation for piercing animal or human skin The metamorphosis is complete Although only a small percentage of the 85 000 species are of medical interest those concerned are of tremendous importance in relation to human health

Classification It is convenient to consider the DIPTERA as falling into three suborders the NEMATOCERA BRACHYCERA and ATHERICERA (or CYCLORRHAPHA) The first two are frequently grouped together as the ORTHORRHAPHA or straight seamed flies the name referring to the man-

of their antennae

Suborder Nematocera

These are the most primitive of the three groups They include the mosquitoes midges and many similar forms Five families of NEMATOCERA are concerned and in all five the females suck blood

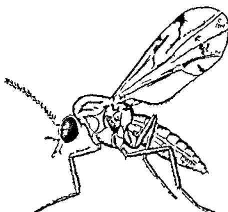


Figure XI 19 *Culicoides* sp Female specimen (After Dampf from Herms *Medical Entomology* by permission of The Macmillan Co)

Family Heleidae (Ceratopogonidae)

This group contains many genera, but only four, *Lasiohelea, Haemophoructus, Leptoconops*, and *Culicoides*, include species which suck the

(finely hairy) wings, which in most species display a characteristic, iridescent spotting (Fig XI 19). The antennae possess 14 segments, the palpi five

Breeding takes place in pools, ponds, slow streams water in hollow stumps, or even in moist soil, depending on the species concerned Fresh water is usually preferred by the aquatic forms, but brackish or salt water is sometimes used The larvae are small, slender, legless, worm like creatures with a distinct brownish head and 12 body segments

Medical Importance. Members of the genus *Culicoides* may be real pests in their own right They are variously known as "punkies," "no-see ums," or "sandflies," the first two names being preferred They attack in the daytime, bite fiercely, and their bites continue to be irritat ing for many days Bites are most numerous at the neckline, the beltline, shoe tops, or where sleeves are rolled up on the arm A nodular, inflamed swelling is produced which in susceptible individuals may become vesicular The vesicle, if ruptured, yields a serous exudate, and the "weeping" continues for several days Conspicuous red scars sometimes persist for weeks (Fig XI 19)

As Vectors. Members of this genus serve as intermediate hosts for two species of roundworms In Africa, British Guiana and New Guinea *Acanthocheilonema perstans* passes seven to nine days as a developing larva in the body of the fly *Culicoides austeni* and *C grahami* are important vectors of this species In the British West Indies *Culicoides furens* Poey functions similarly as the vector of *Mansonella ozzardi*

Family Simuliidae

This family contains approximately 600 species known variously as black flies, buffalo gnats or turkey gnats, and is found throughout the world The females of many species are vicious biters Besides causing discomfort by their bites certain forms (*Simulium damnosum* Theob and *S neavei* Roubaud in Africa, *Eusimulium avidum* Hoffman, *Eusimulium ochraceum* Walker and *E mooseri* Dampf in Mexico and Central America) are common hosts of *Onchocerca volvulus*, a filarial parasite of man At least one species, *Simulium decorum katmai*, has been incriminated as a mechanical vector of tularemia

SIMULIIDAE are small (1 to 5 mm), humpbacked flies with short stubbed antennae of ten or 11 segments The wings are characterized by two or three very heavy veins in the costal region, the remainder of the wing being supported by more delicate veins The palpi have four segments There are no ocelli (Fig XI 20)

Habits and Life History. Black flies breed by preference in rapidly flowing streams the females attaching their eggs to rocks at or beneath the surface of the water Logs and aquatic plants may also be used, and a few species are known to breed in quiet streams and ditches, attaching their eggs to the submerged tips

The larvae have 12 segments
at the posterior end by which the
by cephalic silk glands also aid in this attachment There is in addition a disklike proleg near the anterior end locomotor in function Larval development requires from three to ten weeks depending on the species

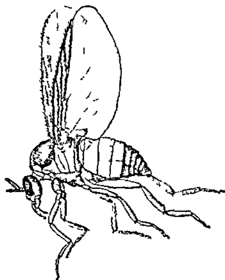


Figure XI 20 *Eusimulium pecuarum* a species of black fly (Redrawn after Garman from Herms Medical Entomology by permission of The Macmillan Co)

and environmental conditions In some species the larvae are black and, when present in large numbers, form a conspicuous blanket on rock surfaces beneath the water

The pupae are likewise aquatic and are enclosed in pocket-like cocoons The pupal stage requires three to six days

Some species produce as many as five or six generations in a single season In latitudes where there is a winter season, both eggs and larvae hibernate

Adult *S damnosum* usually remain close to the breeding area except immediately after a rain, when they may be found as much as 1000 yards away This species bites chiefly from six to eight in the morning and again at dusk, although if there is sufficient shade it will attack at any time during the day Curiously enough, *S damnosum* is reported rarely to bite more than three feet above the ground—hence children placed on tables are seldom if ever bitten A knowledge of these facts is of some importance in avoiding infection with onchocerciasis in regions where *S damnosum* are prevalent

Black Fly Bites. Only the females suck blood The mouthparts consist of six bladelike lancets which are used to make a conspicuous puncture which remains hemorrhagic in character long after the fly has gone Flies of this family usually attack in daylight or full moonlight They may be a terrific pest to fishermen, campers and troops operating near their breeding areas Many species eagerly attack by preference the cheeks, eyes, ears, and neck, although any exposed portion of the body is certain to be bitten This bite itself may be painless, but soon after much pain, swelling and general discomfort occur Lesions may develop which become confluent, vesicular, excoriated, weeping and crusted These may persist for days or a few weeks Satellite adenopathy is a common feature In some persons fever and intestinal disturbances may occur when they are bitten severely Sometimes immunity to the allergic manifestations may develop as a result of repeated exposure to bites Black flies are most annoying in north temperate and subarctic zones, appearing in enormous numbers when conditions favor their development Domestic animals at times are killed by them in the Mississippi valley, following the recession of the spring floods They also are vectors of an important leukocytozoan disease of turkeys in the southeastern states In Alaska a white footed form, *Simulium arcticum*, is a [illegible] ...ns of the year In the early part [illegible] is a pest in Canada and certain [illegible] *columbaczense* (Schiner) is a most important species in Europe, at times causing the death of large numbers of domestic animals and wild game

Treatment of the Bites. The application of dilute alkaline solutions will usually soothe the pain and reduce the swelling In very young children who have been badly bitten, supportive treatment may be required

Family Psychodidae

This important family, the species of which are known variously as moth flies, owl flies or sandflies, is characterized by small size, long legs

and the presence of abundant hair both on wings and body The wing venation is distinctive the longitudinal veins all arising near the base of the wing and lying practically parallel through their course Scarcity of cross veins and a lanceolate outline are also characteristic of psychodid wings The antennae are long and have 12 to 16 segments There are two subfamilies the Psychodinae and Phlebotominae

Psychodinae A single species of the genus *Pericoma* has been reported as biting man in Australia There is also a record of urinary myiasis caused by larvae of the genus *Psychoda* In this instance it is believed that the parasites migrated from the rectum after ingestion with garden soil

Phlebotominae This subfamily is of far greater medical importance than the first More than 60 species are known and in all cases the females suck blood The group includes but one genus *Phlebotomus* Particular species serve as vectors of sandfly fever kala azar cutaneous leishmaniasis espundia oriental sore Carrión disease and possibly tropical ulcer Their bites also cause considerable annoyance and discomfort The group is represented in all warmer regions of the world Fortunately the best known species in the United States (*Phlebotomus vexator*) does not function as a vector of disease (Fig XI 21)

Habits and Life History (with special reference to the genus *Phlebotomus*) Most species breed in rock piles cracks in walls and beneath debris of various kinds In eastern India there is some breeding of *Phlebotomus argentipes* in grass along the margin of streams The habits of *P papatasii* as found in Africa Asia and southern Europe may be cited as typical of the group (see Fig VI 46 p 355)

The small (3 to 5 mm) humpbacked hairy flies deposit their tiny eggs in batches of 50 or more in various dark humid places The larvae hatch in approximately one week and proceed to feed on a variety of organic materials including the feces of lizards and the bodies of their own parents which do not long survive oviposition The larvae are small whitish in color and possess 12 body segments The ninth and tenth abdominal segments are equipped with conspicuous dorsal bristles The three larval stages require a total of approximately 30 days for development and the pupa about ten days more A temperature of 70° to 80° F is most favorable for their growth The adults are poor fliers and do not



Figure XI.21 Male and female of *Phlebotomus papatasi* the vector of sandfly fever (Sabin, Philip and Paul J A M A *125* 1944)

migrate far from the breeding areas Biting occurs at night and it is believed *that the females must have a blood meal* before they can develop their eggs They do not fly if the slightest wind is stirring hence bites may be expected only on quiet nights

Nature of the Bites *Attacking silently* the female *Phlebotomus* seeks out the ankles wrists knees and elbows showing a preference for areas where the skin is particularly delicate or tightly drawn A *painful* stinging sensation is followed by itching which persists for some time Firm whitish wheals which may become pustular and edematous if scratched are characteristic of attacks by *Phlebotomus* If no secondary infection ensues the irritation subsides in a few days though toxemia nausea and rise in temperature have been reported in some cases after numerous bites

Family Culicidae (Mosquitoes)

The CULICIDAE constitute the most important single family of insects *from the standpoint of human health Distributed throughout the world* from the arctic to the tropics mosquitoes from time immemorial have been known as intolerable pests More important than this however is *their role in the transmission of human disease* CULICIDAE *have been* found to act as vectors of filariasis dengue yellow fever the malarias and several of the viral encephalitides

There are *well* over *1500* species of mosquitoes known The family may be distinguished from similar nematocerous DIPTERA (midges crane flies fungus gnats) by two obvious characters 1 The veins of the wings as well as the wing margin are covered by *conspicuous scales* 2 The head bears a conspicuous proboscis which extends either forward or downward when the insect is at rest

Other family characters are as *follows Antennae long and slender* with 15 segments the first usually obscured by the globular second segment (pedicel) male antennae strongly plumose female antennae sparsely hairy ocelli absent wings narrow *thorax without a transverse* V shaped suture on the dorsal surface abdomen long and slender bearing two small caudal cerci in the female and a rather elaborate *hypo*
[illegible] apparat[illegible] in the male

Anophelinae Culicinae
according to the char

Table XI 7 Key to Subfamilies of Culicidae

1 (2) *Female palpi as long as* proboscis or nearly so scutellum almost always evenly rounded wings usually spotted male palpi long clubbed at the tip abdomen not covered with flat scales Proboscis head thorax and abdomen forming a straight line *Anophelinae*

2 (1) Female palpi very short *scutellum variable* wings usually without spot ting male palpi long but not clubbed at tip Profile distinctly hump 3

3 (4)

4 (3)

Subfamily Toxorhynchitinae. ... genus, *Toxorhynchites* (formerly ... are large, iridescent forms, very ... sucks blood The larvae are found chiefly in tree holes, where they feed frequently on other mosquito larvae The group as a whole might therefore be considered beneficial

Subfamily Anophelinae. This important series includes approximately 200 species and is well represented throughout the world, particularly in the tropics It is the consensus that all or practically all species should be included in the one genus *Anopheles,* though various workers recognize certain natural groups to which have been given appropriate subgeneric names, e g , *Stethomyia, Nyssorhynchus, Lophopodomyia, Arthuromyia, Myzomyia, Kerteszia* The genus *Chagasia,* should stand alone, since the scutellum in these forms is trilobed, after the manner of the CULICINAE

Most anophelines should be regarded as potential vectors of malaria, though only some 50 species actually transmit the disease in nature and less than 30 are considered really "good vectors under ordinary circumstances

Habits and Life History of Anophelines (Fig XI 22) The female *Anopheles* deposits her eggs singly or in small groups on the surface of water The anopheline egg is boat shaped and is supported by a pair of rather ornate structures termed *floats* The margin is further ornamented in many species by a beaded "gunwale" termed the *frill* Many species ... the *Anopheles* ... pecies ?), quite ... e separated on the basis of the shape and ornamentation of their eggs Anopheline eggs tend to group together on the surface of water in triangular or stellate patterns with their tips in contact

Larval Characters The eggs hatch in one to two days and the larvae, or "wigglers,' proceed to feed upon various microscopic organisms (bacteria, algae and protozoa) All mosquito larvae possess a broad, flattened head which bears the eyes, the antennae and a pair of conspicuous mouth brushes used for sweeping microorganisms into the mouth The head of an anopheline larva is capable of a rotation of 180° in either direction from the normal, an arrangement which provides for the taking in of surface organisms wherever they may be found

The thorax, like the head, is a flattened structure with little or no evidence of segmentation Legs are absent, but their future locations are indicated by segmental grouping of the thoracic hairs

The abdomen which tapers perceptibly, consists of nine visible segments, the anterior somewhat flattened, the posterior progressively more cylindrical The eighth and ninth abdominal segments differ from the first seven in that they are especially modified for respiratory purposes The two large spiracles, located well back on the dorsal surface of segment eight, are surrounded by five flaps The entire structure overhangs the ninth segment to some extent Just beneath each lateral flap is a crescent shaped structure, the pecten, bearing a variable number

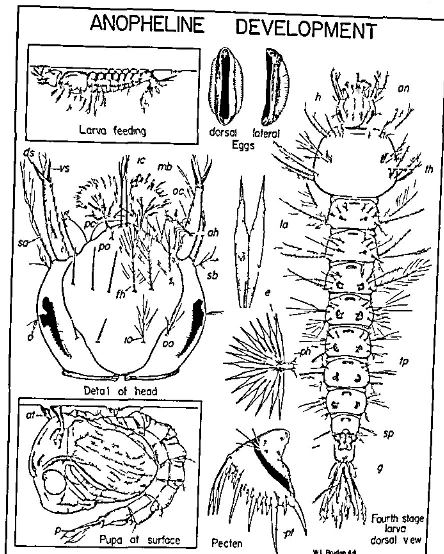


Figure XI 22 All figures except eggs pertain to *Anopheles maculipennis* Meigen Eggs (dorsal and lateral) are from *A gambiae* Giles *ah* antennal hair *an* antenna *at* air trumpet *ds* dorsal saber *e* element of palmate hair *fh* frontal hairs *g* gill *h* head *ic* inner clypeal hair *io* inner occipital hair *la* lateral hair *mb* mouth brush *o* orbital hair *oc* outer clypeal hair *oo* outer occipital hair *p* paddle *pc* preclypeal hair *ph* palmate hair *po* posterior clypeal hair *pt* pecten tooth *sa* subantennal hair *sb* sub basal hair *sp* spiracle *th* thorax *tp* tergal plate *vs* ventral saber

(five or six) of rather conspicuous backwardly directed pecten teeth When the larva rests or feeds at the surface its entire spiracular structure perforates the surface film a condition which requires the larva to lie horizontally and favors feeding on surface organisms In a very few species of *Anopheles* (for example *A turkhudi* List) the spiracular

ture is joined to the body at an angle resulting in an attitude more nbling that of the culicines

osquito larvae pass through four instars the duration of larval life ing from a few days to the entire winter depending on the species climatic conditions As a rule characters sufficiently constant for ification of species are found only in the fourth stage larvae

ie Pupa After completing its development the fourth stage a sheds its skin and becomes a pupa or "tumbler (Fig XI 22) In stage the insect takes no food and for the most part rests quietly he surface of the water its two respiratory trumpets which arise the dorsal surf ertheless have a pair of swi omen When disturbed the pupae go tumbling to the bottom of pool but in a few moments they return to the surface for air In st species but two or three days are required for the complete de pment of the adult characters

upae are not readily classified hence it is the usual practice to await emergence of the adult before attempting to determine the genus species

he Adult Anophelinae The pupal skin serves as a float or raft which the adult may dry its wings and from which it may take off its initial flight Males are distinguishable from females by their hier antennae and by the peculiarly elaborate hypopygium at the terior extremity of the abdomen (Fig XI 23) The palpi of both es of anophelines are long but in the male they are conspicuously bbed at the tip Mating takes place almost immediately

Male mosquitoes live a relatively short time after copulation usually ew weeks at the most The females set out immediately after fertiliza on their quest for a blood meal The majority of anophelines feed preference during the twilight hours of morning and evening al ugh some (*Anopheles atropos*) will attack in direct sunlight as well most species studied it appears necessary for the female to feed on od before she can develop her eggs Mosquitoes deposit their eggs batches throughout the season the total number ranging from 100 500 or more The females continue to feed throughout their life which nonhibernating individuals may be as long as five months A great ny species however hibernate as adult females a fact which makes ssible one practical means of control to seek out their hiding places d destroy them during the dormant period They may be found in e holes caves stables culverts cellars and outhouses A certain ount of moisture combined with semidarkness characterizes the al situation Mosquitoes hibernating in houses occasionally become ive during the winter and seek the warmer rooms for a blood meal

Subfamily Culicinae This the largest natural group of mosquitoes ludes over 1300 species distributed among a large number of genera st known are *Culex Aedes Psorophora Culiseta Mansonia* (*Taeniorhynchus*) and *Wyeomyia* There is a wide variation in structure biology d relation to disease None however is a vector of human malaria

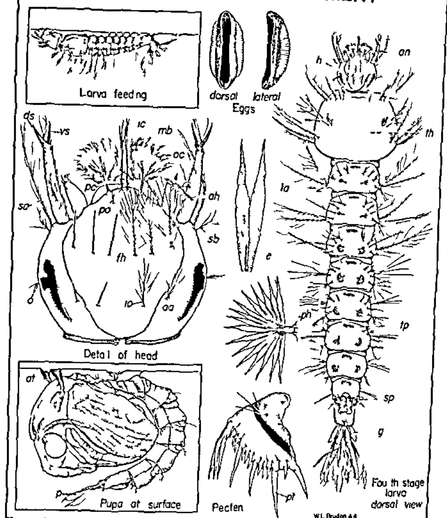


Figure XI 22 All figures except eggs pertain to *Anopheles maculipennis* Meigen Eggs (dorsal and lateral) are from *A gambiae* Giles *ah* antennal hair *an* antenna *at* air trumpet *ds* dorsal saber *e* element of palmate hair *fh* frontal hairs *g* gill *h* head *ic* inner clypeal hair *io* inner occipital hair *la* lateral hair *mb* mouth brush *o* orbital hair *oc* outer clypeal hair *oo* outer occipital hair *p* paddle *pc* preclypeal hair *ph* palmate hair *po* posterior clypeal hair *pt* pecten tooth *sa* subantennal hair *sb* sub basal hair *sp* spiracle *th* thorax *tp* tergal plate *vs* ventral saber

(five or six) of rather conspicuous backwardly directed pecten teeth When the larva rests or feeds at the surface its entire spiracular structure perforates the surface film a condition which requires the larva to lie horizontally and favors feeding on surface organisms In a very few species of *Anopheles* (for example *A turkhudi* List) the spiracular

structure is joined to the body at an angle resulting in an attitu
resembling that of the culicines

Mosquito larvae pass through four instars the duration of lar
ranging from a few days to the entire winter depending on the s
and climatic conditions As a rule characters sufficiently constar
classification of species are found only in the fourth stage larvae

The Pupa After completing its development the fourth s
larva sheds its skin and becomes a pupa or "tumbler" (Fig XI 22)
this stage the insect takes no food and for the most part rests quie
at the surface of the water its two respiratory trumpets which ar
from the dorsal surface of the thorax penetrating the surface film Pup
nevertheless have considerable capacity for motility being equippe
with a pair of swim paddles situated at the posterior extremity of th
abdomen When disturbed the pupae go tumbling to the bottom of
the pool but in a few moments they return to the surface for air In
most species but two or three days are required for the complete de
velopment of the adult characters

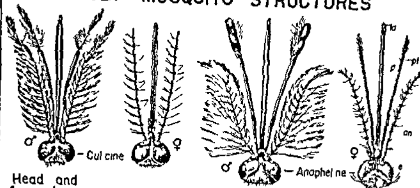
Pupae are not readily classified hence it is the usual practice to await
the emergence of the adult before attempting to determine the genus
or species

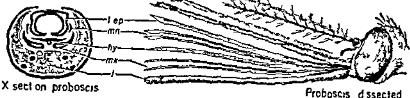
The Adult Anopheline The pupal skin serves as a float or raft
on which the adult may dry its wings and from which it may take off
on its initial flight Males are distinguishable from females by their
bushier antennae and by the peculiarly elaborate hypopygium at the
posterior extremity of the abdomen (Fig XI 23) The palpi of both
sexes of anophelines are long but in the male they are conspicuously
clubbed at the tip Mating takes place almost immediately

Male mosquitoes live a relatively short time after copulation usually
a few weeks at the most The females set out immediately after fertiliza
tion on their quest for a blood meal The majority of anophelines feed
by preference during the twilight hours of morning and evening al
though some (*Anopheles atropos*) will attack in direct sunlight as well
In most species studied it appears necessary for the female to feed on
blood before she can develop her eggs Mosquitoes deposit their eggs
in batches throughout the season the total number ranging from 100
to 500 or more The females continue to feed throughout their life which
in nonhibernating individuals may be as long as five months A great
many species however hibernate as adult females a fact which makes
ossible one practical means of control to seek out their hiding places
d destroy them during the dormant period They may be found in
e holes eaves stables culverts cellars and outhouses A certain
ount of moisture combined with semidarkness characterizes the
l situation Mosquitoes hibernating in houses occasionally become
e during the winter and seek the warmer rooms for a blood meal

bfamily Culicinae This the largest natural group of mosquitoes
les over 1300 species distributed among a large number of genera
nown are *Culex Aedes Psorophora Culiseta Mansonia* (*Taenior*
is) and *Wyeomyia* There is a wide variation in struct
tion to disease None however is a vect

ADULT MOSQUITO STRUCTURES







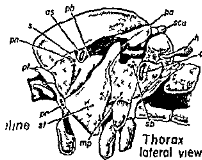


Figure XI 23 Adult mosquito structures *ac* anal cell *al* anal lobe *an* antenna *as* anterior thoracic spiracle *ax* axillary cell *bf* blood canal *cc* costal cell *cl* clasper *cv* costal vein *e* eye *h* halter *hy* hypopharynx *ilc* inner lobe of claspette *is* internal spine *l* labium *la* labellum *lep* labrum epipharynx *ll* leaflets of mesosome *m1 2* marginal cells by number *me* mesosome *mn* mandible *mp* mesepimeral bristles (lower) *mx* maxilla *nt* ninth tergite *olc* outer lobe of claspe e *p* proboscis *pa* pre-alar bristles *pb* postspiracular bristles *pc1 2* poster or cells by number *pl* palpus *pn* pronotal bristles *po* posterior thoracic spiracle *pr* prosternal bristles *ps* parabasal spines *pt* prothoracic bristles *s* spiracular bristles *sa* salivary canal *sb* subalar bristles (upper mesepimerals) *scc* subcostal cell *scu* scutellum *scv* subcostal vein *sm* submarginal cell *sp* side piece *st* sternopleural bristles *ts* terminal spine of clasper 1 2 1 2 2 3 4 1 4 2 5 1 5 2 6 longitudinal veins by number

although certain species of *Culex* are well known vectors of malaria in birds Species of *Culex, Aedes, Mansonia* and *Anopheles* serve as vectors of human filariasis *Aedes aegypti, A albopictus, A scutellaris* and *A*
1900 to be
a number
subspecies
falco are well known in connection with the problem of "jungle yellow fever" in tropical South America *Culex tritaeniorhynchus* is a natural vector of Japanese B encephalitis, *C tarsalis* holds the same relation to St Louis and western equine encephalitis in the United States *Culex pipiens* is a suspected vector of St Louis encephalitis A large number of species belonging to *Culex, Aedes* and *Culiseta* have been shown to be vectors of various viral encephalitides under experimental conditions

Besides this, the world's most famous "pest" mosquitoes fall in the culicine group The northern house mosquito, *Culex pipiens,* and its southern variety, *C p quinquefasciatus,* are well known examples *Aedes taeniorhynchus* breeds in salt marshes from New York to the Guianas as well as from southern California to Peru and the Galapagos Islands *Aedes vexans* is a very troublesome species in the Northeastern States and elsewhere Many others of the same genus (*A spencerii, A punctor, A stimulans, A excrucians, A communis*) play a part in rendering certain otherwise attractive regions quite unsuitable for recreational purposes *Aedes aldrichi* is a particularly serious pest in Washington, British Columbia and Oregon Most members of the genera *Psorophora* and *Mansonia* are fierce biters and cause extreme annoyance when present in significant numbers

Life History. The biology of culicine mosquitoes is similar in many respects to that of the ANOPHELINAE The discussion which follows stresses those features in which the CULICINAE are more or less unique

The Eggs (Fig XI.24) Culicine eggs are laid singly (*Aedes*) or in masses that float on the water (*Culex, Mansonia, Urotaenia, Culiseta*) None, however, is provided with specialized floats as in the case of anopheline eggs

The Larva (Fig XI 25) Culicine larvae, like anophelines, pass through four stages or instars feed on microorganisms by means of mouth brushes and breathe by means of spiracles at the posterior end of the body There are certain differences, however, of a structural character which have a bearing on behavior and manner of feeding and which serve as aids in the recognition of culicine larvae in the field Other structures characterize genera and species and make possible exact classification of the several groups The most distinctive feature of culicine larvae is found on the eighth abdominal segment the dorsal surface of which bears a more or less elongate "siphon" or air tube In certain species (*Culex salinarius*) this structure is almost nine times as long as broad At its extremity are the two spiracles, surrounded by five outwardly directed flaps As in the anophelines the spiracles are thrust above the surface film, but because of the length of the siphon the larva itself rests well below the surface, the typical feeding angle approximating 45 degrees Culicine larvae are not, therefore, surface feeders

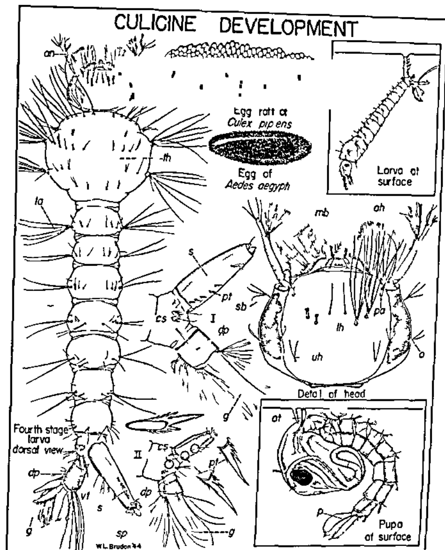


Figure XI 24 All figures except as noted pertain to *Culex pipiens* Linn Anal segments I *Psorophora confinnis* (L Arr) II *Aedes aegypti* (Linn) *ah* antennal hair *an*, antenna *at* air trumpet *cs* comb scales *dp* dorsal plate *g* gill *h* head *la* lateral hairs *lh* upper head hairs *mb* mouth brush *o* orbital hair *p* paddle *pa* preantennal hairs *pt* pecten tooth *s* siphon *sb* sub basal hair *sp* spiracular apparatus *th* thorax *uh* sutural hairs *vt* ventral tufts unlabelled tuft between *lh* and *pa* lower head hair

a fact which makes it relatively difficult to control them by the spreading of poison dusts

An exception to the usual behavior is found in the genus *Mansonia* (for example *M perturbans*) in which the larvae after hatching from the egg rafts attach themselves by their siphons to the stems of aquatic

plants They thus remain below the surface, obtaining oxygen from air spaces in the plant tissue

The breeding sites of *Aedes aegypti* are of particular significance It breeds in cisterns barrels and flower vases—in short, in almost any collection of water (particularly small artificial containers) near dwellings or gathering places of man

The Pupa Culicine pupae have no very distinctive features, save that the cephalothorax tends to be somewhat less massive than in the anophelines, a feature which has a slight effect on the position at the surface *Mansonia*, however, is again exceptional, pupation in this genus taking place below the surface of the water Such pupae obtain oxygen through attachment to plants by their air tubes

The Adult As would be expected in such an extensive group adult culicines display wide diversity in appearance and habits Many are inconspicuously colored, being a uniform dull brown or black, whereas others are brightly marked with gold or silver scales in a variety of patterns Some are diurnal biters, some crepuscular and others nocturnal, some bite at almost all hours of the day or night Some remain close to the site of emergence, others may migrate for 20 miles or more They differ from the anophelines in the form of the palpi (see Table XI 7) and in the humpbacked posture assumed when biting or at rest

Considerations Relating to Both Anophelines and Culicines. *Structural Characteristics of Adult Mosquitoes* There are a number of structural features found in both anophelines and culicines with which the physician should be familiar if he is to attempt identification of the medically important forms or to understand adequately their function in disease transmission

1 BODY As in all insects the body is divided into three essential parts, a head, a thorax composed of three segments that are more or less united, and a flexible abdomen in which eight segments are normally visible

2 HEAD The head, which is nearly spherical, bears the antennae, the compound eyes and the mouthparts, the latter arranged in such a manner as to form a piercing *proboscis* The antennae arise high up on the face between the eyes Each consists of 15 segments, the 13 terminal segments being rather slender and elongate with hairlike projections The antennal hairs are longer and more numerous in males

The proboscis arises from the lower portion of the face and extends forward and downward from the head (more forward in the case of anophelines) The proboscis is flanked on either side by a *palpus* which is approximately as long as the proboscis save in culicine females, where the palpi are exceedingly short Four palpal segments are visible in anophelines, three in culicines Certain species have the palpi ringed and/or tipped with white The proboscis itself consists of six slender stylets (labrum epipharynx, hypopharynx, two mandibles two maxillae) enclosed in a *labial sheath* which terminates distally in a pair of olive shaped *labella* This labial sheath, which is open on the dorsal surface is drawn backward at the time of feeding thus permitting the other

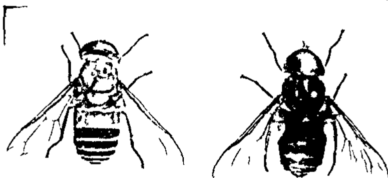


Figure XI 25 The American horsefly *Tabanus americanus* Ford. Female (left) and male (right) 2 × (Courtesy of Dr C B Philip Rocky Mountain Laboratory USPHS)

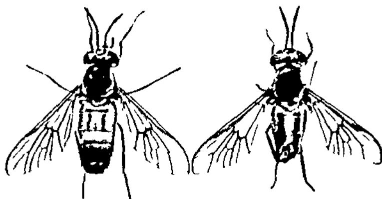


Figure XI 26 Deer fly vectors of loiasis in West Africa *Chrysops silacea* Austen (left) and *C dimidiata* v d Wulp (right) (Courtesy of Dr C B Philip Rocky Mountain Laboratory USPHS)

nished with a conspicuous angular projection The wings are usually uniform in color (Fig XI 25)

The genus *Chrysops* also has a world wide distribution Over 70 species are found in North America alone These are smaller flies rarely exceeding a half inch in length The wings are marked with a dark band across the middle and frequently display a second spot at the tip (Fig XI 26)

The genus *Silvius* rare in North America is abundantly represented in the Australian life zone *Haematopota* scantily represented throughout the world is especially abundant in Africa and in the Orient *Diachlorus* is represented best in South America

Horseflies (PANGONIINAE—*Chrysops Goniops Pangonia Silvius*) may be distinguished from the deerflies (TABANINAE—*Tabanus Haematopota Diachlorus*) by the small spurs at the tips of the hind tibia and the fact that ocelli are usually present

Medical Importance *Bites* The TABANIDAE attack silently and inflict a painful bite The bite is not poisonous but owing to the size of the puncture the site may continue to bleed for some time after the fly has taken its blood meal As in the mosquitoes the proboscis includes a labrum epipharynx and a sheathlike labium Unlike mosquitoes however the labium has labella provided with pseudotracheae which are rasping in function The mandibles are hard sharply pointed cutting blades which serve to pierce and lacerate the skin The maxillae are more complicated and are provided with small recurved teeth The hypopharynx fits against the labrum epipharynx to form a blood canal and is itself provided with a channel the salivary duct The saliva probably functions as an anticoagulant but differs from that secreted by mosquitoes (and other NEMATOCERA) in being nonirritating to man

As Vectors of Disease Two species of mango flies *Chrysops silacea* Austen and *C dimidiata* v d Wulp are proved vectors of *Loa loa* worms in various West African countries

Tabanid flies function also as mechanical vectors of certain important diseases This type of vectorship relates to the habit of feeding on a succession of animal hosts in securing a single blood meal If disturbed while biting they usually proceed at once to a second host carrying on the wet proboscis any microorganisms present in the blood of the first Both anthrax and tularemia may thus be transferred by direct inoculation *Chrysops discalis* is the species most concerned with the transmission of tularemia in six states of the western United States in the U S S R certain species of *Tabanus* are more commonly involved It has been shown that *Chrysops* may remain infective for at least eight to 14 days

Life History Most species of TABANIDAE deposit their eggs in the vicinity of water in many cases gluing them to foliage overhanging a swamp or stream However marginal or emergent rocks are sometimes used while a few species actually prefer dry situations for oviposition From 100 to 700 eggs are deposited in a single cluster the whole being covered by a waterproof secretion Hatching occurs in five to seven days The larvae drop to the ground (or into the water) and develop either in mud moist earth leaf mold or rotting logs the particular ecology depending on the species concerned Tabanid larvae are soft cylindrical with 11 or 12 body segments and a very small head which bears a pair of pointed mandibles Some species (especially *Chrysops*) feed on organic matter of vegetable origin but others (most species of *Tabanus*) feed on insect larvae earthworms snails crustacea and the like A few are cannibalistic There are four to nine larval molts and development requires several months The pupal stage lasts from five days to three weeks larger species tending to require the longer period Emergence from the pupal skin is through a T shaped slit along the dorsum of the thorax as in other typical orthorrhaphous flies The lifespan of adult tabanids is relatively long usually extending from four to eight weeks (Fig XI 26)

Family Rhagionidae (Leptidae)

This family is made up of small to medium sized flies with small heads large eyes long legs and a tapering abdomen Blood sucking forms are found in several genera Only the females bite They attack much as do common species of *Chrysops* (TABANIDAE) with a silent approach The bite is sudden and painful but not poisonous As yet no rhagionid has been incriminated as a transmitter of disease The larval habits vary some species being aquatic others terrestrial Probably all are predaceous Species which have a reputation of being especially annoying to man are included in the genera *Atherix Rhagio Spaniopsis* and *Symphoromyia*

Family Stratiomyiidae

In addition to the two brachycerous families discussed above the STRATIOMYIIDAE or soldier flies are sometimes listed as of medical interest although for very different reasons The adults are of no medical importance Their larvae however which develop normally in decaying fruit vegetables or animal matter are sometimes taken by accident into the alimentary tract of man usually with contaminated food The patient suffers some disturbance of the stomach and intestines and may require treatment to get rid of the maggots *Hermetia illucens* (Linn) is the species most frequently concerned

Suborder Athericera

(Cyclorrhapha)

These are better known flies and constitute a very large group Even conservative taxonomists recognize no fewer than 43 families of which at least 13 are of medical importance Some of the more important members of the Athericera are discussed under the headings of (1) Biting Flies and (2) Myiasis Producing and Filth Flies

Biting Flies of the Athericera

Family Muscidae Important biting flies in this family include species of *Glossina* and *Stomoxys* Two other genera (*Musca* and *Fannia*) are described under myiasis producing and filth flies

Genus Glossina These are the tsetse flies best known because of their role in the transmission of trypanosomes The genus includes some 20 species but not more than three or four are important vectors of human disease *Glossina palpalis* (Rob Desv) is the principal vector of *Trypanosoma gambiense* with *G tachinoides* Westwood in all probability a natural vector also *Trypanosoma rhodesiense* however is trans

mitted by *G morsitans* Westwood and *G swynnertoni* Austen *Glossina morsitans*, the "original" tsetse fly, is the principal vector of nagana, an important and usually fatal trypanosome disease of domestic animals The group is confined to tropical Africa, save that *G tachinoides* has been recorded from Southern Arabia—an example of discontinuous distribution

Tsetse flies are for the most part slender, wasplike insects of brownish coloration The better known forms are very slightly larger than house flies The arista is distinctive, the ornamental bristles being secondarily branched (As in *Stomoxys*, the arista is naked on the under side) The proboscis is elongate and extends forward from the head like a bayonet when not in use It is bulbous at the base and normally is enclosed by the palpi, each of which is grooved internally so that the two palpi, taken together, form a protective sheath When engaged in feeding, the fly lowers the proboscis until the tip makes contact with the skin The palpi, however, continue to extend horizontally The wings of tsetse flies are folded, scissor like, above the abdomen when not being used for flight, and in most species extend a considerable distance beyond the caudal extremity of the fly The fourth longitudinal vein is curiously bent rather near its base, where it is tied to vein three by a very short cross vein This causes the *discal cell* to assume a peculiar shape, resembling somewhat the outline of a butcher s cleaver The presence of this cleaver-shaped cell is diagnostic for the group

Life History Tsetse flies bite in the daytime and both males and females are voracious feeders They by no means confine their attacks to man, all species being parasites primarily of game or reptiles *Glossina tachinoides*, however, maintains itself very well in regions where man is the only available host

A female *Glossina* does not deposit eggs but retains the larvae within her uterus until ready for pupation Only one larva is developed at a time, the fly "giving birth' every ten or 12 days throughout her adult life The individual larva lies with its posterior spiracles in contact with the external os while the mouth remains in proximity to the so-called "milk glands, which are situated near the internal extremity of the uter ine sac All three larval stages are passed in this position, nourishment being derived from the "milk glands," oxygen from the outside When first extruded, the larvae are a creamy white except for the posterior extremity, which is shining black and consists largely of a pair of con spicuous, protruding knobs, each bearing a spiracle The adult fly shows considerable discrimination in selecting an appropriate site for larviposition Loose, pebbly soil, preferably in the shade and not too far from water, seems to be definitely preferred by *G palpalis*, but the larvae of *G morsitans* can survive in hard soil, wood ashes from forest fires, and in other situations The flies appear consistently to avoid contact with ma nure and putrefactive material The larvae, lacking strong mouth hooks, are unable to crawl, but do manage to burrow a few centimeters beneath the surface Pupation usually takes place within an hour, the puparium gradually becoming dark brown in color It may be easily recognized by the conspicuous caudal knobs, reminiscent of the larval state Three to

four weeks are usually sufficient for transformation, although at cool temperatures an even longer period may be required

The several species show marked differences in their choice of environment *Glossina palpalis* breeds by preference on the shores of rivers and lakes, usually in dense undergrowth It is found over an enormous range but is most abundant in West Africa and in the Congo Although it has been stated that *G palpalis* is primarily a reptile feeder, its preferred food seems to be the blood of man It also feeds on many other warmblooded animals, such as mongoose, waterbuck, bushbuck, hippopotamus, monkey, pig and goat *Glossina morsitans* requires more open

sive distribution, but is of greatest importance in Rhodesia, the Belgian Congo and the Sudan *Glossina swynnertoni* tolerates still dryer situations than *G morsitans* It feeds by preference on wild game

The transmission of trypanosomes by tsetse flies may be either mechanical or cyclical, although it is doubtful if the first is ever involved in the infection of the human host Experimental work has shown that the flies are capable of transmitting the trypanosomes mechanically for not more than two days after feeding on an infected animal They then become

cyclic forms It has been demonstrated that trypanosomes are usually injected in large numbers as soon as the fly's proboscis penetrates the skin Thus a *Glossina* which merely "probes," without remaining to feed, may nevertheless transmit infection Adult tsetse flies live from 90 to 250 days or longer

Genus Stomoxys. The best known species is the biting stable fly, dog fly or beach fly, *Stomoxys calcitrans* (Linn) It enjoys practically a worldwide distribution This species somewhat resembles the housefly, *Musca domestica*, but may be distinguished by the fact that the proboscis instead of being expanded distally into a conspicuous pair of oral lobes, is slender at the tip, being adapted as an organ for piercing and sucking The stable fly is also more robust than the housefly and has a broader abdomen *Of the four thoracic stripes, the outside ones are* broken at the middle The abdomen has somewhat of a greenish yellow sheen and shows more or less of a checker board pattern, after the manner of the SARCOPHAGIDAE *The arista is plumose on the upper side only,* whereas in the housefly it is hairy both above and below Also the third and fourth longitudinal veins are much more widely separated at their tips than in *M domestica*

Medical Impor ... be concerned with the spread of poli... in the transmission of human disease ... chanical vectors of anthrax, tetanus ... ore Such transmis

sion is favored if the fly is interrupted during its blood meal and immediately thereafter attacks a second host, the proboscis being still wet with blood On an experimental basis they have also been found capable of the mechanical transmission of certain trypanosomes So far as is known, *T evansi*, the causative agent of surra is transmitted in nature by the activity of biting flies There is record of the larva of *Stomoxys* being found in a lesion on the foot of a stable boy in South Africa Ordinarily, however, the genus is not considered a myiasis producing group

Stomoxys flies are best known however by reason of their painful bites and when present in great numbers have been known to render recreational areas quite uninhabitable and even to cause demoralization among troops (Fig XI 27) Both males and females are vicious biters Fortunately the bites are not poisonous

Life History The adult female requires a number of blood meals before she is able to develop her eggs These are deposited in small batches up to a total of 120 or so before the female seeks another meal A single fly may engage in at least three egg laying episodes during the season with a total production of well over 600 eggs Their favorite breeding places are wet, rotting piles of hay, straw lawn clippings or sea

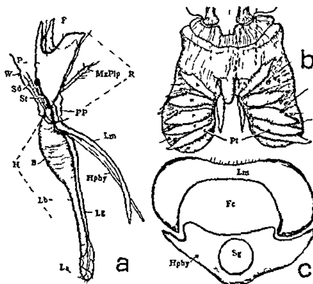


Figure XI.27 Mouthparts of the biting stable fly (*Stomoxys*) *a* Side view of the proboscis. *b* The labella of the proboscis with the prestomal teeth exposed *c* Cross section of the labrum and hypopharynx near the middle of the proboscis *B* swollen base of the labium *F* fulcrum *Fc* food channel *H* haustellum *Hphy* hypopharynx *La* labellum *Lb* labium *Lg* labial gutter *Lm*, labrum *MxPlp* maxillary palpus *P* pharynx *PP* prepharynx *Pt* prestomal teeth *R* rostrum *Sd* salivary duct, *Sg* salivary duct in hypopharynx *St* stipes *W* chitinous membrane (Matheson, R. Medical Entomology 2nd ed Ithaca, N Y., Comstock Publishing Co 1950)

weed Animal manure and vegetable rubbish are also used, but apparently this species has never been known to develop in human excrement

The eggs require from two to five days for hatching and, assuming a summer temperature of 75° to 80° F, the larvae mature in 14 to 21 days The third stage larva seeks a somewhat drier location for pupation, transformation requiring from six to 20 days more, depending on the temperature The life cycle may thus be completed in as short a time as two weeks, though unfavorable conditions may prolong it to seven or eight In North America either the larval or the pupal stage may undergo hibernation

The adult flies tend usually to congregate in sunny places such as on walls or fences, especially in the vicinity of stables and barnyards where a food supply is usually available They appear to feed indiscriminately on cattle, horses, small animals and man In warm weather they are said to require two meals a day On dark days (as also at night) they seek shelter in houses, barns and sheds Before and during storms they are prone to bite fiercely, thereby creating the impression that meteorologic conditions have caused the housefly to become a biter This concept is entirely in error, as the housefly has no means of perforating the skin

Nonbiting Flies of the Athericera Producing Myiasis

The many species of cyclorraphous flies which may produce myiasis and/or breed in filth are included in this group

Myiasis. A classification of the types of myiasis according to the portion of the body affected is frequently of greater value to the physician than an arrangement based on the obligatory nature of the parasitism, *since his interest is clinical rather than biological* The outline given below illustrates the various sites of infestation with typical examples

1 Specific cutaneous myiasis
   a Superficial–Example *Auchmeromyia luteola*
   b Typical

2
   discharges)
   a. Usually ophthalamic–Examples *Oestrus ovis Rhinoestrus purpureus (nasalis)*
   b Miscellaneous–Examples *Callitroga hominivorax Chrysomyia bezziana* Vari- (see below)

3 odorous skin regard
   ina Callitroga macel

4 *Tubifera (Eristalis)*

5 Genitourinary myiasis
   a By migration from alimentary tract–Example *Psychoda*
   b By oviposition in sexual apertures–Examples *Fannia Sarcophaga carnaria*

A summary of the information regarding the important myiasis producing species is given in Table XI 8 Some of the larvae are illustrated in Fig XI 28 More detailed discussion of some of the species is presented following this figure











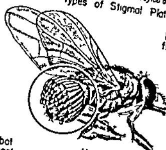




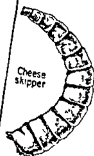




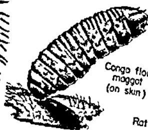












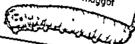


Figure XI.28 Dipterous larvae causing myiasis in man.

Table XI 8. Types of Myiasis in Man

SPECIFIC MYIASIS

COMMON NAME OF SPECIES	SCIENTIFIC NAME (OR GROUP)	GEOGRAPHIC DISTRIBUTION	RELATION TO HOST	CLINICAL PICTURE	RECOMMENDED PROCEDURE	REMARKS
Congo floor maggot	*Auchmeromyia luteola*	Tropical Africa	Sucks blood at night only	Perforation of skin	Avoid contaminated ground and native huts	Larvae hide in ground during daytime
Tumbu fly	*Cordylobia anthropophaga*	Tropical Africa	Young larvae invade unbroken skin (often of feet)	Furuncular swelling, with sloughing	Avoid contact with soil mineral oil hastens emergence of larvae from tissue	Larvae leave normally after 8 9 days
Human botfly	*Dermatobia hominis*	Tropical South America, Central America, Mexico	Larvae invade exposed areas of skin	Throbbing pain pruritus, oozing of blood	Adhesive tape petroleum jelly on cotton surgical removal	Fly glues eggs to mosquito or other carrier
Horse botfly	*Gasterophilus* spp	Worldwide	Larvae wander beneath skin galleries small superficial	Shifting swollen skin lesions (creeping eruption) not serious	Remove larvae using aseptic precautions	Three species are normal parasites in gut of horse
Cattle botflies (ox warbles)	*Hypoderma* spp	Worldwide	Larvae beneath skin galleries large deep rarely cause ophthalmomyiasis interna	Larvae less mot le than above, lesions sometimes furuncular may be serious	Remove larvae using aseptic precautions	Are normal parasites in backs of cattle
Sheep botflies	*Oestrus ovis*	Worldwide	Pharynx nose conjunctival sac	Great irritation may cause optic atrophy	Remove from eye by instruments from nares by irrigation	Are normal parasites in head passages of sheep
Head botfly of horses	*Rhinoestrus purpureus*	Southern and eastern Europe N Africa Asia Minor	Conjunctival sac etc.	Inflammation of conjunctiva or lachrymal duct	Remove with aseptic precautions	Russian gadfly normal in head passages of horse
Rodent botfly	*Cuterebra* sp.	Widespread (specific record from Virginia U S A)	Maxillary sinuses	Pain congestion	Remove with aseptic precautions	Human infection very rare
Primary screw worm fly	*Callitroga hominivorax*	Western hemisphere (tropical subtropical and warm temperate)	Larvae invade nose ears sinuses wounds (rarely unbroken skin)	Produce festering deep disfiguring wounds	Remove by aid of irrigations (chloroform in milk or oil)	Mortality 8%
Old World screw worm fly	*Chrysomya bezziana*	Oriental and Ethiopian life zones	Gums, nares, ears, conjunctiva, sinuses, vagina or lesion any where on body	Erode bone produce foul smelling lesions	Remove with aseptic precautions	Usually leave wound in 7 14 days

Flesh flies	*Wohlfahrtia magnifica* *W. vigil* *W. meigenii* (New World form)	Mediterranean, Near *East, U S S R.* Nearctic Western U S.	Invades nose, ears, wounds of all types Invades unbroken skin Invades unbroken skin	Produces disfiguring wounds Furuncular lesions Furuncular lesions	Remove by aid of irrigations Remove with aseptic precautions Remove with aseptic precautions	*May cause death* Parasitizes babies especially in neck region *Parasitizes* babies especially in neck region *All* are larviparous
SEMISPECIFIC MYIASIS						
Common screw *worm fly*	*Callitroga macellaria*	Western hemisphere widespread	Invades lesions, wounds (especially if malodorous)	Often complicates lesions of primary screw *worm fly*	Remove by irrigation or mechanically	Normal in decaying flesh, really saprozoic
Green bottle flies	*Lucilia sericata* *Lucilia* spp	Worldwide	Invade wounds cutaneous ulcers, malodorous apertures	Complicate existing lesions induce purulent conditions	Removal with aseptic precautions	Usually attack only diseased tissue formerly used in surgery treatment of osteomyelitis
Blue bottle flies	*Calliphora* spp *Cynomyia* spp	Worldwide	Invade wounds, cutaneous ulcers, malodorous apertures	Complicate existing lesions induce purulent conditions	Removal, with aseptic precautions	Usually attack only diseased tissue
Black bottle flies	*Phormia regina* *Phormia* spp	Worldwide	Invade wounds, cutaneous ulcers, malodorous apertures	Complicate existing lesions induce purulent conditions	Removal, with aseptic precautions	Usually attack *only diseased* tissue formerly used in treatment of osteomyelitis
Flesh flies	*Sarcophaga* spp.	Worldwide	Invade wounds, cutaneous ulcers, malodorous apertures may penetrate unbroken skin	May produce serious disfigurement	Removal with aseptic precautions	Many species are larviparous
Stable fly	*Stomoxys calcitrans*	Worldwide (specific record from S Africa)	Probably invades open wound	Aggravates existing lesion	Removal with aseptic precautions	Very rare in man
Non-biting stable fly	*Muscina* spp.	Worldwide	Probably invades open *wound*	Aggravates existing *lesion*	Removal with aseptic *precautions*	Presumably a secondary *invader*
Houseflies	*Musca* spp.	Worldwide	Probably invades open wound	Aggravates existing lesion	Removal with aseptic precautions	Presumably a secondary invader

Table XI 8 Types of Myiasis in Man (Continued)

COMMON NAME OR SPECIES	SCIENTIFIC NAME (OR GROUP)	GEOGRAPHIC DISTRIBUTION	RELATION TO HOST	CLINICAL PICTURE	RECOMMENDED PROCEDURE	REMARKS
ACCIDENTAL MYIASIS—INTESTINAL						
Houseflies	*Musca crassirostris*	India	Inhabit various portions of gastrointestinal tract	Symptoms variable distress pain anorexia nausea vomiting, cramps, diarrhea, melena	Vermifuges and purges sometimes effective (spontaneous passage of larvae rather common)	Infection acquired by eating or drinking or by flies depositing eggs or larvae on anus during defecation
Houseflies Green bottle flies Blue bottle flies Flesh flies *Latrine flies *Lesser housefly Non biting stable fly Cheese skippers Rat tail maggot Other syrphid flies	*M domestica* *Lucilia* spp *Calliphora* spp Fam. Sarcophagidae *Fannia scalaris* *F canicularis* *Muscina stabulans* *Piophila casei* *Tubifera (Eristalis)* spp *Helophilus* sp	More or less generally distributed throughout the world				
Soldier fly Flies of the screw worm group Wood gnats Fruit flies	*Hermetia illucens* (Fam Stratiomyidae) *Callitroga putoria* *C chloropyga* *Rhyphus fenestralis* (Fam Anisopodidae) *D n h n* *Calobata* sp (Fam Micropezidae)	Records few and scattering	Inhabit various portions of gastrointestinal tract	Symptoms variable distress pain anorexia, nausea vomiting cramps, diarrhea, melena rarely ulcerative colitis	Vermifuges and purges sometimes effective (spontaneous passage of larvae rather common)	Infection acquired by eating or drinking or by flies depositing eggs or larvae on anus during defecation
Hump back fly	*Megaselia (Aphiochaeta) scalaris* (Fam Phoridae) *M rufipes*	West Indies N A Belgian Congo India Burma, widespread (except Australian region)	Gastrointestinal tract larvae pupae and flies passed in feces	Intestinal distress	Vermifuges and purges helpful	Also recorded from wounds *M scalaris* more common in man than *M rufipes*
ACCIDENTAL MYIASIS—GENITOURINARY						
Houseflies Cheese skippers Moth flies Rat tail maggots Other syrphid flies Latrine flies Green bottle flies Non biting stable flies Flesh flies Blue bottle flies	*Musca domestica* *Piophila casei* *Psychoda* sp *Tubifera (Eristalis)* sp *Syrphus* sp *Sepsis* sp (Fam Sepsidae) *Fannia* spp *Lucilia* sp *Muscina* sp *Sarcophaga carnaria* *Sarcophaga* sp *Calliphora* sp	Records few and scattered	Urinary tract including bladder genital passages of females	Obstruction dysuria hematuria pyuria strangury	Careful removal by use of cystoscope sometimes successful (spontaneous passage of larvae is common)	Infection acquired by migration of larvae from intestinal tract or by flies depositing eggs or larvae on genital aperture, especially of females

* [illegible] reported causative agents of intestinal myiasis in man

Family Muscidae

Including Anthyomiidae of Some Authors

This family includes the housefly, *Musca domestica,* and a considerable number of related forms Almost every conceivable medical relationship exists within the group Some, like *Stomoxys,* are confirmed blood suckers, i e, external parasites in the adult state Others (*Glossina*) combine the same habit with the cyclical transmission of blood parasites (trypanosomes)

Filth breeding (and filth feeding) species act as mechanical vectors of bacteria, protozoal cysts and helminth eggs Larvae of the same or other species not infrequently develop within the body of man, causing various types of myiasis, the nature of the parasitism depending on the adaptability of the species concerned Whereas the genus *Musca* is worldwide in its distribution, other groups, like *Glossina,* are sharply limited to particular continents or parts thereof Two important genera (*Musca* and *Fannia*) are discussed here Material on *Glossina* and *Stomoxys* has been presented on pages 734–738

Genus Musca. The best known species in this large genus is the much publicized housefly or typhoid fly, *Musca domestica* Linn, referred to above Of all flies taken in kitchens and pantries over a large portion of the United States, 98 8 per cent proved to be of this species In certain parts of the world, notably in Egypt, a variety, *Musca domestica vicina,* largely replaces the typical form The same subspecies is common in India, as is *Musca nebulo* *Musca sorbens* is a house visitor in Indonesia This species, which occurs both in Ethiopian and Oriental life zones, shows great proclivity for feeding about the eyes, particularly if the latter are infected For this reason it is believed responsible for the transmission of much trachoma and conjunctivitis

The adults are approximately one-fourth of an inch in length, and are of a gray-brown color, save that the abdomen tends to be yellowish on the sides and still lighter below Four longitudinal black stripes extend the length of the thorax (exclusive of scutellum) on the dorsal side The eyes are reddish brown The antennae are typically muscoid, extending vertically downward, within the facial depression The third segment bears a typical dorsal *arista,* plumose practically to the tip The wings diverge at an angle of nearly 60° when in the resting position Vein 4 is bent forward near the extremity so as to contact the margin in advance of the apex and fairly close to longitudinal Vein 3

Medical Importance Because of their habits flies distribute an immense number of microorganisms There is laboratory evidence for the transmission of 30 different diseases Cholera, typhoid, amebic and bacillary dysentery, various diarrheas tetanus, anthrax, trachoma, yaws, and certain helminthic infections (by eggs) are among the diseases listed

In all this the vectorship of the fly is mechanical rather than cyclical in nature There are at least four ways, however, in which the organisms may be conveyed

1 By the general body surface and especially the hairs of the feet and

legs Particularly important are the sticky hairs of the *pulvilli* (pad like structures situated close to the tarsal claws)

2 By feces the organisms having passed through the alimentary canal of the fly This is sometimes accompanied by *multiplication of the bacteria* in the gut

3 By the vomitus Flies habitually regurgitate a portion of the contents of their crop prior to the ingestion of food

4 By *metamorphosis organisms* taken up by the larval form frequently being present in the body of the adult fly The eggs of *Ascaris* likewise the spores of anthrax and tetanus may be transmitted in this way

Life History The curved whitish eggs are deposited in manure garbage and other organic materials Horse manure seems to be preferred but cow, pig and chicken manure as well as human excrement are often used A single female usually deposits about 120 eggs in a batch and individuals have been known to lay several batches with the total approaching 2400 Incubation requires eight to 24 hours depending on the temperature

The larvae which measure only about 2 mm at the time of hatching grow rapidly molt three times and under favorable conditions reach maturity in six or seven days As in many other muscoid species house fly larvae are blind footless maggots with a pair of very small chitinized mouth hooks protruding downward from the tapering anterior end The *mouth hooks are really part of a somewhat elaborate pharyngeal skeleton* largely concealed within the first two or three segments of the body The larva is made up of 12 visible (13 actual) segments the last bearing an obliquely tilted stigmal plate on which a pair of conspicuous dark colored spiracles may be easily observed Maggots will not develop if the temperature is too hot, as at the center of a manure pile neither can they survive if the medium becomes too dry as in manure spread thinly upon an open field These facts have a bearing on practical methods of control

The pupal stage is passed inside the last larval skin which becomes tightly contracted and takes on a reddish brown color A pupal case formed in this manner is termed a *puparium* Three to six days are required for transformation after which the fly emerges by pushing off a circular cap (operculum) at the anterior end This is accomplished by the pressure of a specialized bladder like structure the ptilinum which however is withdrawn into the head a few hours after emergence

After emergence from the puparium the adult flies require from two to 24 days before they are able to deposit eggs The latter is unusual In general the warmer *the temperature the shorter the preoviposition* period Many generations may occur in one year therefore control measures to be effective must be applied relatively early in the season Otherwise the problem becomes exceedingly difficult to handle and even partially successful measures involve enormous labor and expense

Behavior of the Adult Fly Flies normally migrate but little from their place of origin but studies on marked individuals indicate that they may travel as far as ten to 14 miles either with across or against the wind

The fly s proboscis has three well marked regions a basal portion the

rostrum which bears two small palpi an intermediate portion the haustellum and a terminal sucking mechanism composed of two lobes or labella between which is a cleft (prestomum) leading directly to the food canal Under ordinary circumstances however food material does not enter this aperture but is drawn in through the "interbifid grooves" of the pseudotracheae which run transversely across the free surface of the labella. These tiny orifices will not admit an object greater than 0 006 mm in diameter hence a majority of individuals only rarely take up items as large as pollen grains (Fig XI 29)

The act of feeding involves first a flattening of the oval lobes against the surface to be explored Next the fly regurgitates a portion of the contents of its crop the vomitus serving to dissolve or at least emulsify the substance on which the fly is about to feed This habit provides for

the insect has fed recently on human excrement When the food particles have passed into solution (or suspension) the fly sucks up the mixture of vomitus and nourishment but the clean up is incomplete and many contaminative organisms of course remain

While feeding the fly may also defecate at least once and thus provides additional opportunity for infective organisms to leave its body In general however vomit specks are probably much more important than fecal specks in the dissemination of disease since by actual count they have been found to be from ten to 100 times as numerous as the latter

A fly population will be contaminated in inverse proportion to the degree of sanitation practiced in the homes and in the streets In regions where the human feces are deposited directly upon the ground the fly

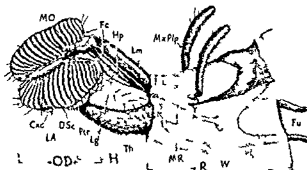


Figure XI.29 Mouthparts of a nonbiting fly the housefly (*Musca*) *R* Rostrum, *H* haustellum, *OD* oral disc *MO* mouth opening *Cxc* a main collecting channel of the pseudotracheae *DSc*, discal sclerite *Fc* food channel between the hypopharynx (*Hp*) and ...

population becomes heavily laden, both externally and internally, with whatever infective organisms the human population may be harboring

It has been shown that dysentery bacilli remain alive in the intestine of the fly at least four days and that cysts of *Entamoeba histolytica* may survive for 49 hours

It should be pointed out that flies of other genera (*Fannia, Muscina*) and also of other families (CALLIPHORIDAE, SARCOPHAGIDAE) frequently breed and feed in filthy material but that such species do not as a rule tend to enter houses or visit human food as frequently as does the house fly They are therefore less likely to be a menace to human health To be an important transmitter of infection a species must (1) feed on human excrement, (2) visit houses and contaminate food and drink Unless a species does both, it need give us no great concern

Genus *Fannia*. The group to which this genus belongs is usually considered as constituting a separate family, the ANTHOMYIIDAE, distinguishable from the MUSCIDAE by the fact that the third and fourth longitudinal veins are more widely separated in the margin However since this is the only genus of sufficient medical importance to be considered in this work, we may conveniently regard the group as falling in the family MUSCIDAE, in the larger sense along with *Musca, Glossina* and *Stomoxys*

Two species are of importance to human health, *Fannia canicularis* (Linn), the so called lesser housefly and *F scalaris* (Fabr), the latrine fly Both are widely distributed through all but the colder regions of the world

Fannia canicularis is a small grayish fly distinguishable from the house fly not only by the wing character described above but also by its naked antennal arista and three dorsal thoracic stripes The legs are black and the halteres distinctly yellow They do not, however, tend to congregate on human food as eagerly as do houseflies The eggs of this species are laid on either decaying vegetable matter or animal manure, including human excrement Piles of grass, especially lawn clippings furnish an ideal breeding site The eggs hatch in 24 hours and the larvae require at least seven days for development They may be very readily identified by the large spinelike processes borne both dorsally and laterally by practically every segment of the body The lateral processes are double or multiple Unlike typical muscoid maggots these larvae are greatest in diameter at the middle, both anterior and posterior extremities being bluntly tapered The entire larva is noticeably flattened dorsoventrally The pupal stage lasts approximately one week

Fannia scalaris, the latrine fly, is very similar to the above species but is usually a bit larger The life history is similar to that of *F canicularis*, but the fly seems to prefer excrement to vegetable matter as a site for oviposition

The larvae of both species have been repeatedly recorded as causing both intestinal and urinary myiasis in man (Fig XI 28) The parasites apparently gain access to the human host in two ways

1 By way of the mouth, along with decaying fruit or on food soiled

with human or other excrement Either the eggs or the developing larvae are apparently infective

2 By exposure of the anus or genitals in such a manner as to give the flies an opportunity to deposit eggs in or near these apertures This might occur either while the person is using an open privy or while resting or sleeping in a more or less unclothed condition Urinary myiasis as caused by these species probably always originates by the external route rather than by migration through the tissues from the alimentary canal Infection of the genitourinary tract is more common in females than in males

Symptoms of Infection by Fannia Larvae GASTRIC MYIASIS The presence of any considerable number of larvae in the stomach usually causes nausea sharp pain vertigo and sometimes violent vomiting This often results in the expulsion of some of the larvae on which diagnosis may be based

INTESTINAL MYIASIS Pain diarrhea and hemorrhage from the anus are possible indications of the presence of larvae in the intestinal tract A certain number of larvae may eventually be expelled in the feces spontaneously

GENITOURINARY MYIASIS Victims of infection in these organs have been known to manifest albuminuria dysuria hematuria and pyuria Spontaneous passage of the larvae with complete termination of symptoms is common

Genus Muscina The genus *Muscina* (nonbiting stable fly) is sometimes of medical importance Larvae of this genus have been found infesting open wounds (probably as secondary invaders) and have also been taken from the human intestinal tract

Family Syrphidae (Hover flies)

The rat tail maggots of the genera *Tubifera* (*Eristalis*) and *Helophilus* are capable of adapting themselves to the human intestinal tract Nasal myiasis due to larvae of this group has also been recorded The drinking of water from foul ditches or puddles is probably responsible for most

resemblance to bees (see Fig XI 28)

Family Drosophilidae

Known variously as fruit flies pomace flies or banana flies most members of this family breed in spoiled fruit grape pomace and similar organic matter The accidental ingestion of their larvae may result in infection of the alimentary tract Both adults and larvae are very small (3 to 4 mm long)

Family Piophilidae

The larva of *Piophila casei* the well known "cheese skipper" has been repeatedly recorded as causing intestinal myiasis in man The maggot

which attains a length of more than 5 mm is rather conical being pointed anteriorly and truncate posteriorly The body is shining and smooth but the ventral traveling folds are roughened and the posterior segment bears four small fleshy protuberances Occasionally the larvae will pupate and develop into adults in the intestine of man The patient usually suffers a severe colic with headache, vertigo and nausea The feces may contain blood (Fig XI 28)

Family Chloropidae (= Oscinidae)

Life History *Hippelates pusio* is a small (2 mm) blackish fly with yellowish legs (Fig XI 30) The adult flies are exceedingly fond of pus blood sebaceous material and lachrymal secretions Though brushed away they return again and again until thoroughly satiated While they are not able to pierce the integument they do possess tiny spines on the labellum by means of which they are able to make minute multiple incisions in mucous membranes It is during this process of scarification that infective organisms may be introduced The white curved fluted eggs are deposited by preference in loose cultivated soil with a high organic content

Medical interest attaches to the behavior of the adults, several species of which habitually feed on sores and especially the secretions of the human eye Outstanding in this respect is *Hippelates pusio* Loew the eye gnat" of the Coachella Valley, California where it serves as the mechanical vector of epidemic conjunctivitis usually of a severe follicular type The species however, is not confined to the western states having been known for more than 50 years as a transmitter of conjunctivitis in Florida and elsewhere Besides serving as vectors of conjunctivitis eye gnats may be of medical importance in other ways *H pallipes* is believed to be a mechanical vector of yaws in Jamaica *H flavipes* probably functions in a similar capacity in Haiti There is no cyclical development

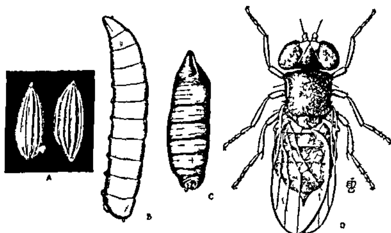


Figure XI 30 The eye gnat *Hippelates pusio* A Eggs B larva C pupa D adult (Courtesy of Dr D G Hall, Am J Hyg)

of the parasites, the spirochetes being digested in the stomach of the fly *Siphunculina funicola* de Meyere is the common eye fly of India, where it spreads both conjunctivitis and Naga sore Trachoma may likewise be transmitted by chloropid flies

Family Gasterophilidae (Botflies, in part)

These are the botflies of horses, asses and related hosts The larvae live normally within the alimentary tract of these animals, being attached by their mouth hooks to the gastric or intestinal mucosa The exact location varies in accordance with the species concerned

These flies deposit their eggs on the skin, hair or lips of the animals The larvae then either burrow in or are swallowed, eventually arriving at their definitive location

The distribution is worldwide Human infection, though apparently accidental, is nevertheless fairly common, especially in warmer regions In man, however, the larvae usually remain subcutaneous in position where they cause a "creeping eruption somewhat similar to that caused by the larvae of the dog hookworm, *Ancylostoma braziliense*

The adult flies of this group range from 9 to 18 mm in length and are characterized by stout bodies rather densely clothed with fine hair They somewhat resemble honeybees True bristles are absent The antennae lie well within the facial depression, the aristae are bare

Life History. These flies are unable to bite, in fact they take very little food of any kind They are nevertheless exceedingly annoying to horses They glue their triangular (stalked) eggs to the hairs of the host animal, hatching being stimulated (at least in certain species) by friction against the teeth or tongue, as the horse bites or licks its legs The egg of each species has a distinctive shape Even the newly hatched larvae possess rather conspicuous, backwardly directed spines on most

place in dry horse dung or loose soil The flies copulate soon after emergence and in a temperate climate oviposition normally takes place in early summer The life cycle requires about a year

Symptoms of Parasitism in Man When eggs are laid on the human host the first stage larvae burrow into the skin as far as the stratum germinativum after which they wander aimlessly about producing a form of cutaneous myiasis They may survive for months A tortuous inflammatory line marks the path of migration the larvae being found just in advance of the progressive inflammation The condition is commonly termed "larva migrans" *Gasterophilus intestinalis* (De Geer) is the spe-

not uncommon

Diagnosis and Treatment The larva is usually found just in advance of the inflammatory line It may be rendered visible by the application of a small amount of mineral oil, which causes the skin of the patient to

become transparent By use of a lens the backwardly directed spines segmentally arranged may be readily demonstrated thereby establishing the dipterous nature of the parasite Hookworm larvae have no such structures Surgical extraction is relatively easy

Family Oestridae (Botflies concluded)

For practical purposes the botflies other than the GASTEROPHILIDAE may be grouped in a single family the OESTRIDAE.* *In these forms the* fourth longitudinal vein bends sharply forward either joining vein three before the margin (*Oestrus*) or terminating in close proximity to it (*Dermatobia*) The mouthparts are vestigial As in the GASTEROPHILIDAE *it is only the* larval stage which is of medical importance Most species normally parasitize animal hosts the human subject being attacked but rarely The following genera will be discussed *Dermatobia Oestrus* and *Hypoderma*

Genus Dermatobia The only recognized species is the so-called human botfly *D hominis* (Linn) This species is native to Central and South America and Mexico where its larvae are found parasitic in the skin of various mammals and birds as well as man Domestic cattle are very frequently parasitized The young larva is sometimes called *ver macaque* later instars being known under the designation *torcel* or *berne* Another common name is *ver moyocuil* The adult fly is approximately 15 mm long and is generally a brownish gray color The abdomen however is of a distinctly bluish cast especially when viewed in reflected light The legs and face are orange yellow

Life History The adult fly does not seek its host directly almost always utilizing some species of insect for the transmission of its eggs Mosquitoes of the genus *Psorophora* (*Janthinosoma*) particularly *P lutzii* (Theobald) and *P ferox* Humboldt seem to be favorite carrier hosts in Central America and Northern South America In Brazil biting flies such as *Stomoxys* and *Siphona* (*Haematobia*) are made use of and even *Musca* and *Anthomyia* as well as certain species of ticks are sometimes found with *Dermatobia* eggs glued fast to their bodies The *Dermatobia* female usually captures the mosquito (or other species) in flight and [illegible] to the ab

face close against the botfly s thorax Upon release the burdened carrier then goes its own way in the case of blood sucking forms to seek a blood meal *from an appropriate warm blooded host in the case of* non-blood sucking species perhaps to rest on vertebrate skin (Fig XI 28)

The eggs which contain fully developed embryos are stimulated to hatch by the warmth of the host s body the eggs being so placed that the end through which the larva emerges is directed away from the body of the carrier host In penetrating the skin of the vertebrate host the

interest or [illegible]
included w th the OESTRIDAE in the broader sense

young larvae frequently make use of the feeding puncture of the carrier species but are capable of perforating the unbroken surface with their own mouthparts

The larvae once established do not migrate but remain in situ where they give rise to a boil like swelling open at the top The larva whose anterior segments become robust is much attenuated posteriorly particularly for the duration of the second instar The caudal extremity bears a pair of large functional spiracles which remain in contact with the exterior thus insuring an adequate supply of air (Fig XI 28) The parasites become larger fatter and considerably more grublike as time goes on Conspicuous backwardly directed spines adorn most of the forward segments Development requires from 50 to 100 days after which the parasites extricate themselves from the host tissue drop to the ground and pupate

Symptoms of Infection There is usually no sensation during the actual penetration of the skin by the first stage larvae During the first week there may be pruritus particularly at night and by the second week a serous exudate is frequently observed After this the lesion begins to resemble a small furuncle which increases in size and becomes exceedingly painful by the beginning of the fourth week continuing so until larval development is completed Muscular soreness and stiffness may be continuously present and the attempts of the parasite to rotate on its own axis frequently result in excruciating pain at the point of infection There is considerable destruction of local tissue and the lesion may even resemble a local streptococcus infection with associated lymphangitis Inguinal lymphadenitis may likewise be evident particularly if the lesion is located on or near the ankle Prior to the emergence of the larva the swelling may attain the size of a pigeon s egg but emergence itself seems to involve almost no pain or sensation of any sort

Treatment and Removal of the Larva Several methods for removal of the parasites have been employed Natives squeeze out the larva after opening the boil and applying tobacco juice A good modern technique involves the following steps

1 Injection of a 2 per cent aqueous solution of procaine with a hypodermic needle both in and around the lesion as a preliminary procedure Larva and host are thus both anesthetized 2 The larva is then exposed by a linear incision 4 or 5 cm long if necessary The parasite may be removed by forceps Irrigation with sterile saline followed by packing with a one-to one mixture of sulfanilamide and sulfathiazole is recommended 3 If little or no secondary infection is present the wound may be closed with interrupted dermal sutures otherwise it is best to apply a tight dry dressing without suturing

Genus Oestrus This genus is of special interest because of the common head bot of sheep *Oestrus ovis* Linn whose larvae develop normally in the sinuses and nasal passages of the above mentioned host On occasion however the adult flies deposit first stage larvae in the human eye where they give rise to a painful and dangerous ophthalmomyiasis They are also known to invade the nasal passages and sometimes the

pharynx The species is worldwide in distribution occurring wherever sheep and goats are raised (Fig XI 28)

Life History The fly normally deposits living maggots in the nostril of sheep and goats The young larvae work their way into the nasal and frontal sinuses where they may accumulate in such numbers as to cause their hosts considerable pain sometimes causing death The symptoms may resemble "gid (True gid of sheep is caused by a larval tapeworm of the genus *Multiceps*) Larviposition takes place any time during the summer or early fall the larvae remaining within the host until the following spring when they have attained a length of 25 to 30 mm They then wriggle out of the nostrils of the host and fall to the ground where they undergo pupation Transformation requires from three to seven weeks

Symptoms of Ophthalmic Infection in Man Almost immediately after larviposition the patient is conscious of severe pain as the tiny larva proceeds to attach to the conjunctival membrane by means of its curving mouth hooks The first stage maggot (Fig XI 28) has exceedingly large mouth hooks in proportion to its size and the injury to the host tissue may be severe If the larva is not removed at once a progressive conjunctivitis develops leading in some cases to loss of sight Infection by *Oestrus ovis* is to some extent an occupational condition shepherds being commonly attacked especially in Israel

Treatment Anesthesia may be effected by dropping cocaine into the eye after which the larvae may be removed either by irrigation or by use of forceps

Genus Hypoderma These are the cattle botflies or ox warbles Two species are especially well known *H lineata* (Villers) and *H bovis* Linn Both occur widely in Europe Asia and North America the second being restricted to somewhat more northerly latitudes The grubs are found normally in tumorous swellings on the backs of cattle but may occur as parasites of horses and sometimes occur in man

Life History The hairy beelike fly deposits up to 800 eggs usually on the hairs of the cattle The hatched larvae bore through the skin of the host migrate through the tissues and eventually localize beneath the skin of the back Later they escape through the skin and drop to the ground to pupate The life cycle requires one full year

Symptoms of Infection in Man The act of oviposition usually goes unnoticed Several days later soreness and swelling may be apparent the center of irritation shifting in accordance with the migrations of the larvae There seems to be a tendency for the larvae to migrate upward "against the pull of gravity" a tropism which should bring them to their definitive location in the normal host but which leads merely to aimless wandering when the host is man whose upright posture seems to disorient the parasites Migrations from knee to chin and from groin to scalp have been recorded

Once the larvae approach the surface of the skin they usually move but little Perforation may thus take place long before the larva is mature which provides an opportunity for the recognition and removal of the parasite Considerable muscular stiffness with hernialike swellings has

been reported in specific cases Surgical removal with the usual aseptic precautions is the recommended procedure If the larvae are full grown it is possible to distinguish the species In *H bovis* the last two segments are entirely devoid of spines, in *H lineata* only the last segment has no spines *Hypoderma* rarely parasitizes man, but when present can be far more serious than the more commonly encountered parasitism by *Gasterophilus*

Family Calliphoridae* (Blowflies and Others)

This widely distributed family is made up of medium to large, robust, rather bristly flies, characterized for the most part by metallic green, blue or yellowish coloration, at least on the abdominal segments None of these species is a blood sucker in the adult stage, all, however, may function as mechanical vectors of various disease organisms by means of their feces vomitus or body hairs Of particular interest is that many of their larvae produce myiasis in man some as specific parasites other in a semispecific or accidental capacity The following genera will be discussed in turn *Auchmeromyia, Cordylobia, Callitroga* (= *Cochliomyia*) *Chrysomyia, Lucilia* (= *Phaenicia*), *Phormia, Calliphora*

Genus Auchmeromyia. The genus is well known from the Congo floor maggot *Auchmeromyia luteola* (Fabr) a common species in tropical Africa The large brownish yellow flies deposit batches of eggs on the floor of native huts on sleeping mats or on dry sand previously contaminated with human excreta The larvae are extremely resistant to dryness and can survive long periods (30 days) without food They remain hidden during the day but become active at night, when they wander about in search of a blood meal With their mouth hooks and body spines they perforate the skin of persons sleeping on the ground With the anterior segments more or less embedded in the tissues they engorge (Fig XI 28) This process requires from 15 to 20 minutes They then detach and once more go into hiding in the soil or dust If hosts are available for nightly feeding, larval development may be accomplished in as brief a period as two weeks, otherwise as long as three months may be required Pupation takes place on or in the ground and requires about 12 days Parasitism is obligatory with this species Such a type of myiasis differs from all others in that the larva remains external

[illegible]

is a

s nar

rower front and more rounded abdomen Another distinguishing feature is that in *C anthropophaga* all visible abdominal segments are of ap

* This family is with difficulty separated from the family SARCOPHAGIDAE (flesh flies). In fact the two are sometimes combined under the family name METOPIIDAE. The latter name however is rare in medical literature and it is felt that separate treatment of the groups will better serve the purpose of this work

proximately the same length whereas in *A luteola the second visible* segment is noticeably longer than any of the others This species is confined entirely to the African continent where it is known under the name of Tumbu fly The female deposits her eggs in polluted soil or on clothing which bears an odor of perspiration The larvae hatch in 24 to 48 hours and proceed to seek an appropriate mammalian host After penetrating the unbroken skin (usually the feet in man) they develop very much like *Dermatobia hominis* the location of each parasite being marked by the presence of a furuncular swelling Sloughing and even gangrene may be observed particularly when a number of parasites localize in a restricted area Fortunately only eight to ten days are required for larval development the parasites having by that time attained a length of 12 to 15 mm Pupation takes place in the ground The adults emerge from 22 to 24 days later

Treatment and Prophylaxis The application of mineral oil will usually cause the larvae to loosen their hold and leave the host re gardless *of the stage of development Since rats constitute the principal* reservoir for these parasites rodent control is of importance in holding the species in check It may be noted that animals which have supported an infection appear to be relatively immune to subsequent attacks

Genus Callitroga (= Cochliomyia) These are the screw worm flies of the western hemisphere The adults are metallic green in color resembling somewhat ordinary green bottle flies (*Lucilia*) but may be recognized by the dark stripes on the dorsal surface of the thorax Two species are of medical interest *C hominivorax* (Coquerel) and *C macel laria* (Fabr) of which the first though less common is of far greater importance from a medical standpoint

Callitroga hominivorax is the primary screw worm of animals and man and is found in the southern United States and throughout the American tropics The flies are attracted by *any open wound or discharging* aperture depositing their eggs in batches on the skin close by A single fly may deposit as many as 300 eggs in five minutes time The larvae *may either enter the wound or in* thin skinned animals such as rabbits and guinea pigs penetrate the unbroken skin It is believed that they cannot perforate the unbroken skin of man This species does not con fine its activity to necrotic areas preferring to burrow deep into healthy tissue sometimes penetrating cartilage and even bone Deep festering extremely malodorous wounds are characteristic of the infection Nasal and aural infections due to this species are truly dangerous penetration of the brain especially by way of the middle ear being a not *uncom* mon occurrence

The larvae require up to three weeks for development depending on the *conditions encountered When full grown* they are pinkish and about two thirds of an inch long Advanced larvae will mature even after the death of the animal Pupation takes place in the soil Transformation requires from one week (in summer) to nearly two months (in colder weather)

Symptoms of Infection in Man Nasal infection is the most com mon but frequently goes undiagnosed for some time There may be

much local swelling, and the patient usually complains of intense pain and a sensation of crawling. Delirium is not uncommon. Rarely some of the larvae may be sneezed out or emerge spontaneously. With proper illumination the physician usually may see the larvae in situ. Their mouthparts are normally embedded deep in the tissues, the posterior extremity and its spiracles being left free to insure a supply of air (Fig. XI.31).

Treatment of Nasal Myiasis

Three steps are involved:

1. Anesthetize the larvae and the mucous membrane by applying benzol, ether or chloroform, either on a cotton pledget or with an atomizer. Block nostrils with dry cotton for 2 or 3 minutes.

Irrigation with 20 per cent chloroform in sweet milk or 15 per cent chloroform in light mineral or vegetable oil is also an effective method of accomplishing anesthesia.

2. Remove the larvae with forceps and have the patient blow his nose. Special care should be taken to avoid rupturing exposed blood vessels.

3. Give aftercare appropriate to any similar wound.

Two or three applications of the anesthetic may be necessary in the case of extensive infection.

Protection of the Individual

1. All persons who wish to sleep during the day in regions where screw worms occur should be protected by screens or bed nets. Such



Figure XI.31 Infection with *Calliroga hominivorax*. Over 230 screw worm larvae were removed from this patient's nasal passages. (Courtesy Dr. W. E. Dove and associates, Bureau of Entomology and Plant Quarantine, U. S. Dept. of Agriculture.)

protection is especially important for patients who are wounded or who have active nasal catarrh or discharges from the eyes

2 Any bandages or clothing stained with blood should be promptly removed and destroyed

3 Adequate screening of hospitals is essential

Genus Chrysomyia This genus is similar to *Callitroga* in that all species are medium sized flies of bright metallic coloration The genus is confined to Africa Australia parts of Asia and various islands, including the Philippines *Chrysomyia bezziana* (Villeneuve), known generally as the Old World screw worm fly, is similar in its habits to *Callitroga hominivorax* being not only an important pest of sheep but also the *causative agent of serious and disfiguring myiasis in man especially in* Asia The maggots may occur in any portion of the body but ophthalmic infections are particularly serious Erosion of bone is not uncommon The larvae develop very rapidly and are ready for pupation on the sixth or seventh day The adult fly is characterized by the presence of transverse abdominal bands

Genus Lucilia (Green Bottle Flies) These are medium sized metallic green or bluish flies The genus is very widespread The females normally deposit their eggs on meat or dead animals Not infrequently however they utilize open wounds or malodorous body apertures *Lucilia sericata* (Meigen) sometimes referred to as the genus *Phaenicia* is an important sheep maggot in the British Isles and elsewhere damaging healthy tissue and endangering the life of animals Usually the larvae restrict their activities to wholly diseased tissues This species was formerly used in the treatment of osteomyelitis The same species be*cause of its abundance and filth feeding hab ts is frequently* important in the mechanical transmission of intestinal diseases *Lucilia caesar* (Linn) is a well known species in the Old World while *L illustris* occupies a similar position in North America *Lucilia cuprina* is the common sheep *maggot of Australia Larvae of this genus have been* known to cause various types of myiasis in man including cutaneous intestinal and genitourinary infections

Genus Phormia (Black Bottle Flies) Flies of this group may be either shiny black blue or green *A well known species is the black* blowfly *Phormia regina* (Meig) normally a breeder in decaying meat but capable of causing traumatic myiasis in man

Genus Calliphora (Blue Bottle Flies) These are rather large flies of various metallic coloration the common pattern consisting of a *grayish thorax and an abdomen of some shade of* blue As in related genera blue bottles breed usually in the bodies of dead animals and doubtless have some sanitary value in hastening the destruction of putrefactive material The larvae of some forms however develop as parasites on nestling birds *Calliphora vicina* Robineau Desvoidy (= *C erythro*

[illegible] members of

[illegible] may be of some

[illegible] with *Lucilia*

larvae of this genus may cause nasal cutaneous gastrointestinal or genitourinary myiasis in man

Family Sarcophagidae* (So-called Flesh Flies)

This family includes a considerable number of small to large flies, most of which present a remarkable uniformity of appearance The prevailing color is gray, although a golden pollinose sheen is not infrequently observed on the abdominal segments Dark longitudinal lines characterize the dorsal surface of the thorax In almost all species the dorsal surface of the abdomen presents a striking "checkerboard" appearance Two genera, *Sarcophaga* and *Wohlfahrtia* are of medical importance

Genus Sarcophaga. This is a very large genus the adults of which are either filth feeders or flower feeders The larvae are found in a variety of situations, many feeding on the bodies of dead insects carrion or animal excrement *Sarcophaga haemorrhoidalis* (Fallen) is a proved agent of intestinal myiasis, the eggs or larvae presumably being ingested along with food (fruit, meat) to which flies have access Other species are undoubtedly capable of similar adaptation *Sarcophaga carnaria* (Linn) seems to prefer the vaginal orifice for oviposition

As in the following genus larvae have been taken from wounds cutaneous ulcers, nasal passages and sinuses the adult flies being attracted in all cases by a malodorous discharge *Sarcophaga dux* may cause tissue myiasis and S *ruficornis* has been recovered from wounds *Sarcophaga fuscicauda* (*peregrina*) has been known to cause extensive traumatic myiasis of the face

Genus Wohlfahrtia. This genus is very similar to the genus *Sarcophaga* except that the checkerboard pattern of the abdomen gives way to something like a black spotting in most of the species *Wohlfahrtia vigil* (Walk) and *W opaca* (Coquillet) in North America also *W magnifica* (Schin) in Europe and the Near East are frequent causative agents of myiasis of the integument and sense organs All three are larviparous, and first stage maggots of *W vigil* and *W opaca* (= *W meigenii*), at least are capable of penetrating the unbroken skin

Treatment and Removal of Sarcophagid Larvae Proceed as outlined for similar infections by larvae of *Muscidae, Oestridae, Gasterophilidae* and *Calliphoridae* (pp 740–742)

* See note on family CALLIPHORIDAE p 753

75

Control of Arthropods of Medical Importance

Carroll N Smith

Measures for the control of arthropods are of three types—mechanical or cultural biologic and chemical Chemical control measures are by far the most widely used although they rarely provide a permanent *solution to a problem as mechanical* measures sometimes do *Biologic* control measures have been highly successful against some agricultural pests but as yet they have had only a small place in the control of medically important arthropods

Mechanical and Cultural Control

Mechanical and cultural methods play an important part in the control of arthropods injurious to man Some mosquito problems may be solved by elimination of the larval breeding places by various types of water management—ditching draining impounding or filling These are often called permanent control measures although filling is the only method that requires no attention after installation Proper measures for the disposal of sewage garbage and manure are of the utmost importance in the prevention of fly breeding Elimination of trash piles rat harborages and birds nests near human habitations will reduce annoyance from such pests as scorpions centipedes and various bird and mammal parasites Screens are an important protective measure against flying insects The first step in any insect control campaign be it nationwide or restricted to a single building should be a survey to determine the source of breeding and infestation If the breeding places can be reduced or eliminated by mechanical means such measures should be taken first If breeding cannot be eliminated attention should be given to biologic and chemical methods

Biologic Control

Biologic control measures in the accepted meaning of the term have not been used widely for the control of medically important arthropods It should be remembered however that all animals are subject to attack by predators and parasites which reduce their numbers to some degree However the important pest species are well adapted to survive these attacks and still reproduce in destructive numbers Biologic control meas

ures refer to the
of the natural en
essful against co
particularly *Gambusia* have been introduced into cisterns and other water containers to control mosquito larvae

The screw worm fly *Callitroga hominivorax* has been eradicated from certain areas by the use of gamma irradiation (Cobalt 60) to sterilize the male flies These flies are released from the air over infested areas in numbers that exceed those of the normal population Males of this species mate repeatedly females only once Females that mate with sterile males lay infertile eggs and hence are eliminated as far as maintenance of the species is concerned

Chemical Control

Chemical control measures have been expanded enormously since the beginning of World War II Such measures depend on the introduction of damaging chemicals into the arthropod s environment Insecticides may function as contact poisons entering the insect s system through the integument (rotenone in flea powder) as stomach poisons (lead arsenate in foliage sprays) as fumigants (methyl bromide) or in any combination of these ways DDT may function as a contact and stomach poison lindane in all three ways

Types of Insecticides Most modern insecticides are either inorganic compounds botanicals chlorinated hydrocarbons or organophosphorus compounds Inorganic compounds including arsenicals fluorine compounds and other chemicals were most widely used before World War II these are still useful although they have largely been superseded by synthetic organic compounds The botanicals are represented by the pyrethrins which are obtained from pyrethrum flowers and rotenone from the roots of derris or cube During and after World War II the chlorinated hydrocarbons such as DDT lindane chlordane dieldrin methoxychlor and others came into widespread use and because of their greater effectiveness it was possible to carry out extensive control programs Later the organophosphorus compounds including such materials as malathion dicapthon parathion TEPP Diazinon and others came into general use

Residual Action of Insecticides Since the advent of DDT much emphasis has been placed on the residual action of insecticides It is only with compounds such as DDT which not only remain unchanged on treated surfaces for long periods but which are *effective by contact at extremely low concentrations* that the full value of residual action can be realized

Residual sprays differ from contact sprays or space sprays in that they are applied to surfaces on which the insects are expected to walk or rest at some later time Contact sprays are applied with the objective of striking and killing the insects present at the time of treatment The insecticides used in residual sprays must therefore be durable chemically stable under all conditions of temperature and humidity and effective in minute quantities so that the insects will pick up a toxic dose

through a bri
met these rec
of malaria ca
ings with DI
populations through a single application of DDT powder, and the control
of bed by single applications
of DDT as been controlled by
employ

Resistance to Insecticides. Individual insects within a species vary in their susceptibility to an insecticide, just as they vary in all other respects When an insecticide application fails to kill all the insects in a population, the survivors will represent the most resistant fraction of the population, and their progeny may be more resistant than an average group Such resistance is enhanced by cross breeding among the survivors This has occurred with many of the insects of medical importance exposed to the chlorinated hydrocarbons, and is now occurring with the organophosphorus compounds (Table XI 9)

When resistance first developed to DDT, other chlorinated hydrocarbons were substituted, but many of the insects quickly became resistant to them also These were then superseded by certain of the organophosphorus compounds

Table XI.9. **Medically Important Arthropods Reported as Showing Resistance to One or More Insecticides**

MOSQUITOS
- *Aedes dorsalis**
- *Aedes aegypti**
- *Aedes nigromaculis**
- *Aedes sollicitans**
- *Aedes taeniorhynchus**
- *Anopheles gambiae**
- *Anopheles maculipennis**
- *Anopheles quadrimaculatus**
- *Anopheles sacharovi**
- *Anopheles stephensi**
- *Anopheles subpictus**
- *Anopheles sundaicus**
- *Anopheles superpictus*
- *Culex molestus**
- *Culex p quinquefasciatus (fatigans)**
- *Culex pipiens**
- *Culex tarsalis**
- *Psorophora confinnis**
- *Psorophora discolor**

OTHER DIPTERA
- *Chrysomyia putoria**
- *Culicoides furens**
- *Glyptotendipes paripes**
- *Musca domestica**
- *Musca vicina**
- *Psychoda alternata*

HEMIPTERA
- *Cimex lectularius**
- *Cimex hemipterus**
- *Triatoma infestans*

COCKROACHES
- *Blattella germanica**
- *Blatta orientalis*

LICE
- *Pediculus humanus humanus**

TICKS
- *Rhipicephalus sanguineus**

FLEAS
- *Ceratophyllus fasciatus*
- *Ceratophyllus londinensis*
- *Ctenocephalides felis*
- *Pulex irritans*
- *Rhopalopsyllus clavicula*
- *Xenopsylla cheopis*

* Species in which resistance has been confirmed by laboratory tests

Methods of Application of Insecticides Insecticides may be applied as sprays aerosols (including fogs and smokes) dusts granules or baits Sprays may be applied either for immediate contact or for residual action as solutions or suspensions The latter may be prepared from emulsions or wettable powders The solvent most commonly used for indoor sprays is deodorized kerosene which is noninjurious to nearly all of the materials found in the home Fuel oil is usually used as the solvent for solution sprays to be applied outdoors When used as recommended for example in airplane sprays at 1 to 3 quarts per acre it is not injurious however excessive dosages may injure foliage

The emulsifiable concentrates used to make emulsion sprays usually contain 25 to 50 per cent of an insecticide and 5 to 10 per cent of an emulsifier in a noninjurious solvent They may be used in homes on surfaces that water will not injure in animal shelters and on foliage They are economical reduce transportation problems in large scale programs and leave satisfactory residues on most surfaces

Wettable powders usually contain 50 to 75 per cent of the insecticide on an inert carrier with a wetting agent They are economical and easy to transport They are more satisfactory than solutions or emulsions for the treatment of clay mud or concrete surfaces and are useful for treating foliage barns or other surfaces

Aerosols are extremely fine particles of insecticides that remain suspended in the air for considerable periods They may be produced by liquified gas generators (the common aerosol bomb) smoke generators or as mechanically generated fine mists They are applied indoors or outdoors for immediate contact action only although they do leave minimal residual deposits in closed buildings When used outdoors they are dependent on air currents to carry them to the insects and can only

for the treatment of poultry manure to prevent fly breeding as louse powders and in other special problems They do not cling well to most vertical surfaces but may have residual action on horizontal surfaces as in the treatment of cockroach harborages

Insecticide granules are usually made with an inorganic carrier such as attapulgite montmorillonite or vermiculite The granules may range in size from 16-mesh to 60 mesh depending upon the application equipment terrain and cover They usually contain fairly low concentrations of insecticide 10 per cent or less and are usually dispersed at rates of 5 to 20 lb per acre In medical entomology the granules are especially useful for aerial treatments of vegetated marshes for the control of mosquito tabanid or sandfly (*Culicoides*) larvae Granules penetrate the foliage better and can be dispersed when wind conditions are too unfavorable for the use of dusts or sprays

Baits have been used widely for the control of house flies and to a lesser extent for the control of cockroaches and ants They consist of an

Aedes aegypti and *A albopictus* are daylight biters *Culex pipiens* and *C p quinquefasciatus* feed either at night or in darkened rooms *Aedes stimulans*, *A excrucians* and several others prefer late afternoon for feeding but *Aedes spencerii* attacks in bright sunshine

Culicines in general show a greater flight range than anophelines *Aedes sollicitans* has been known to migrate as much as forty miles *Aedes vexans*, at least ten *Aedes cantator* and *A taeniorhynchus* are also known for their migrations Some (*A aldrichi*) restrict their migrations to wooded areas Domesticated and semi domesticated species, however, remain fairly close to their breeding grounds

The same contact and residual sprays used to control anophelines in buildings will also control culicine adults In addition, since many culicine species breed in tremendous numbers and cause severe annoyance, operations are often conducted to eliminate them from outdoor areas Entire cities or military installations are often treated from the air or with ground equipment Such applications provide only temporary relief, but are helpful where the area to be protected is surrounded by extensive breeding areas that cannot be treated with larvicides DDT, BHC and malathion, in the order named, are the insecticides used most commonly for this purpose Sprays, dusts, smokes and fogs have all been used with good effect

Anti Larval Measures

All members of the four genera *Culex*, *Mansonia*, *Uranotaenia* and *Culiseta*, deposit their eggs in rafts on the surface of the water (Fig XI 24) In the case of *Culex pipiens* each female, fresh from hibernation, lays 100 to 400 eggs in a single mass

In most other genera of culicines the eggs are laid singly in water, near water, or where water is likely to be Species of *Psorophora* deposit eggs d [illegible]
remain [illegible]
finally [illegible]
ing as a rule, only a few days

Most species of *Aedes* leave their eggs during the summer in the bottoms of dried out pools, swamps and marshes Such eggs remain dormant throughout the fall and winter (even if submerged), not hatching until the following spring A few species of *Aedes*, however, produce at least two broods a year *Aedes varipalpus* and *A triseriatus* usually seek tree holes in which to deposit their eggs *Aedes aegypti* being a domestic species, oviposits on or just above the surface of water in various small containers near the habitation of man These eggs, unlike certain species mentioned above, hatch very quickly Where temperature permits, breeding of *A aegypti* goes on throughout the year This species cannot survive outside of tropical and subtropical latitudes, though it may migrate into temperate regions and reproduce successfully during the summer months

It is convenient to classify culicines into three general groups on the basis of the type of habitat selected for breeding purposes

1 Domesticated species which like *Aedes aegypti* *Culex pipiens* and *C p quinquefasciatus* breed in and about human dwellings

2 Semidomesticated species which may breed either close to human habitations or in other situations as opportunity affords

3 Wild species which avoid the habitations of man being found in salt brackish or fresh water marshes in swamps woodlands prairies or other natural situations

fore classed as wild

divided into "spring b

America *A stimulans* *A canadensis* and *A cinereus* are examples of the first group *A sollicitans* *A taeniorhynchus* and *A cantator* of the second

Most of the larvicides that are effective against anophelines are used for the control of culicines and such water management procedures as ditching impounding draining and filling are the principal measures for the control of many species Efficient irrigation practices can reduce or eliminate some of the worst culicine problems

The most important culicine is *Aedes aegypti* which is known to be one of the principal vectors of dengue and yellow fever It also serves as a vector of filariasis certain of the encephalitides and may mechanically transmit tularemia

Aedes aegypti. This species is a day flier until it obtains its first blood meal after which it feeds and flies principally at night Consequently certain additional precautions are necessary if adequate control is to be achieved

In areas where *A aegypti* is prevalent all buildings especially hospital wards should be sprayed with a contact insecticide two or three times daily Fox holes and outdoor resting areas for troops should be treated at least once a day as conditions permit Persons in mosquito infested areas should remain fully clothed with sleeves rolled down and should make use of mosquito repellents At night they should sleep under mosquito nets If these are not available or if one is required to be out of doors at night repellents should be used

Control of *A aegypti* centers around measures that are applicable to urban communities as this mosquito is a household breeder Its larvae are found in cisterns barrels clogged or defective roof gutters tin cans buckets or in any depression in which water remains for several days Furthermore this species may oviposit inside houses in water pitchers slop jars flower bowls and the like Ornamental garden pools unless adequately stocked with fish are potentially dangerous Flower vases in cemeteries are often the source of mosquitoes

In all such instances the larvae may be controlled by the judicious app

con

(sc

tors to enter all dwellings at frequent intervals in order to detect and destroy larvae of *A aegypti* Eradication programs are based on treating all possible breeding places and adjacent surfaces especially walls with 5 per cent DDT solution suspension or emulsion Because of its lon

residual action treatments may be spaced three or more months apart. However DDT resistant *A aegypti* have been found for such strains BHC or dieldrin may be used

Control of Other Culicines As previously pointed out there are other culicine species which serve as vectors of disease certain species of *Culex* are good vectors of Japanese B or endemic encephalitis and of filariasis bancrofti In the United States culicines transmit the virus of western equine encephalomyelitis In the *Mansonia* group (including the subgenus *Mansonioides*) are vectors of the filarial worm *Wuchereria malayi* In addition to these many species of *Culex* and *Aedes* are exceedingly important as human pests Some coastal regions are virtually uninhabitable by reason of the tremendous number of salt marsh breeding forms

Control measures against other culicines are similar to those already described for *Aedes* and *Anopheles*

The genus *Mansonia* presents a special problem in that the larvae and pupae of these mosquitoes secure their oxygen from the subsurface stems of aquatic plants such as water lettuce (*Pistia*) and are therefore not readily affected by surface treatment Development is slow requiring nearly a year In areas where both plants and mosquitoes are abundant control may best be achieved by destruction of the plants

Fly Control

Two principles are important to keep in mind 1 If possible begin early in the season before the fly population abounds 2 Concentrate primarily on prevention of breeding rather than on destruction of the adult fly

The elimination of fly breeding areas involves at least three separate problems

The Disposal of Animal Manure The following procedures are recommended

1 Daily spreading of the manure on agricultural land Where possible this is the best method of all since it allows no breeding opportunity to exist and utilizes the fertilizer at the most favorable time for benefiting the soil

2 Storage of the manure in fly tight boxes or pits preferably of concrete with wooden doors above which of course are kept closed except when material is being put into the pit A fly trap should be placed at the top to catch the flies of the inevitable small infestation

3 The piling of the manure in cubes or "ricks with vertical sides The heat of decomposition drives the maggots to the surface where they may be treated in various ways

4 Treatment by use of chemicals

a In the absence of resistance most of the chlorinated hydrocarbons serve as effective larvicides Chlordane BHC dieldrin and aldrin are effective at dosages of 50 to 100 mgm per square foot Continued use of these compounds however is likely to result in the rapid development of resistance

b Several of the organophosphorus insecticides will control housefly

larvae that are resistant to chlorinated hydrocarbons The most effectiv
is Diazinon, but malathion, parathion and others are also useful Th
should be applied at 100 to 200 mgm per square foot

c Hellebore (must be fresh) one-half pound in ten gallons of wate
The preparation should be allowed to stand for 24 hours and may then b
sprinkled over the manure with a watering pot This amount is sufficie
for the treatment of eight bushels

d Borax, 11 ounces in from two to ten gallons of water, dependin
on the amount of moisture already present in the material to be treate
This amount also is sufficient to treat eight bushels and may be applie
by sprinkling There is a drawback to this method in that the borax ma
prove toxic to crops Manure spread on fields, less than 15 tons of treat
manure per acre, is considered to be safe

5 "Maggot trap" method of storage A slatted platform is arrange
over a concrete pit which contains a certain amount of water Heav
wetting of the manure will drive the maggots out, whereupon they fa
into the water and are drowned Third stage maggots, seeking a place i
which to pupate, will likewise be captured Frequent cleaning or flushin
of the pit should be provided for This is especially necessary in malar
ous areas, where a neglected pit provides an ideal situation for the deve
opment of certain species of mosquitoes

It is needless to say that stables should be properly constructed an
should receive thorough daily care

Disposal of Human Excrement This involves

1 The installation of a sanitary sewage disposal system (if possible

2 The screening of all privies and latrines with special attention t
cracks, ventilation devices and other apertures likely to be overlooke

3 Sprinkling of borax over exposed feces at least every three or fou

Disposal of Garbage 1 For temporary storage of garbage, water
tight metal cans with accurately fitting covers should be used

2 For ultimate disposal nothing is superior to incineration, if equip
ment is available

3 Conservation uses (require special care and supervision) Thes
fall into four general categories

a Reduction in special plants, with salvage of useful chemical sub
stances *This is practical only in very large municipalities where volum*
warrants the capital outlay A market for the commercial products is als
necessary

b Grinding of bones for fertilizer

c Feeding of edible portions to swine Hog farms are always a menac
in the matter of fly production and should be located beyond flight rang
of the community or camp

d Composting with a view to future agricultural use This is ver

4 Burial of all garbage is usually very satisfactory if there is thorough compaction of both the garbage and the soil covering The latter should be not less than one foot in depth, preferably two

Measures against the Adult Flies In spite of conscientious efforts to prevent the development of the larvae, at least a few flies will succeed in attaining maturity Again (especially in the military service), the medical officer may find himself confronted with a problem of fly borne disease in a region where he has had no opportunity to face the situation early in the season, and consequently finds a large number of flies already on hand The following procedures are of proved value

SCREENS In humid climates copper, bronze, alloy or plastic must be used, to avoid corrosion In a very dry climate, however, galvanized screening is usually adequate Painting of the screens also provides protection against weathering A mesh of 14 wires to the inch will exclude houseflies, but it is better to use at least 18 mesh because of the desirability of controlling smaller insects at the same time Accurate fitting of both screen doors and window screens is important Doors should open outward Foods likely to attract flies, such as hung meats, should, of course, be screened as well

FLY TRAPS A tremendous reduction in the fly population may be effected by the judicious placing of fly traps of suitable construction A conical type, made of screen and baited with molasses milk, or waste fruit, works very well The flies enter from below and, as a result of their tendency to fly upward toward the light pass through the narrow aperture at the apex of the cone into an upper chamber from which they are unable to escape Frequent emptying of traps is desirable Captured living flies should be killed before removal either with hot water or by means of a spray Fly traps function best when set in the sun, in a place protected from the wind

proved of great value in controlling flies about stables and dairy barns

SPRAYS. The application of sprays either by hand spray guns or power sprayers is a useful procedure when flies are abundant Such sprays are of two types, which may be combined, if desired

1 Aerosols "Bombs" containing pyrethrum, freon, and a synergist with or without DDT, may be employed to produce a floating vapor, consisting of exceedingly fine particles very useful in killing insects in a small, enclosed space The interiors of airplanes may be effectively treated in this way

2 Space or Contact Sprays These act as contact poisons and are especially useful indoors (see page 772)

3 Residual Sprays In these sprays the toxic agent is applied to walls of buildings, both inside and out, to screens, and in the vicinity of garbage cans, privies, manure piles, and other places where flies are prone to congregate (see page 773) Some of the organophosphorus compounds, particularly malathion and Diazinon provide effective control of houseflies when applied as residual insecticides in the same manner

as DDT However the periods of protection obtained without retreatment are much shorter ranging from a few days to several weeks In a few localities flies have developed resistance to these compounds also In some areas houseflies have been controlled in barns by suspending cords or strips of cloth saturated with parathion or Diazinon which kill flies resting on the cords by the residual action of the chemical

BAITS Formalin arsenicals and other materials have been used in fly baits but the most effective formulations have contained the fast acting organophosphorus compounds Malathion Diazinon Dipterex and others are used at concentrations of 1 to 2 per cent in dry or liquid baits Dry baits may consist merely of granulated sugar with the insecticide or of the insecticide and sugar applied to corn meal sand or other granular material Liquid baits consist of 10 to 50 per cent of molasses or syrup in water with the insecticide These baits are scattered or sprinkled liberally on floors or other surfaces where flies congregate to feed or rest They cause spectacularly quick reductions but must be reapplied every day while infestations persist

Attempts to provide longer lasting bait treatments have been made by applying heavy syrup baits that dry to a varnish like surface on sites where flies rest Bait stations consisting of 4 inch square paddles covered with a mixture of sugar sand insecticide and gelatin have also been used These do not provide such rapid reduction as the scatter baits but when used in adequate numbers have given reasonably good control for periods of several weeks or months

Control of Other Arthropods

Methods for the chemical control of the various arthropods of medical importance are summarized in Table XI 10 It must be remembered that priority should be given to sanitation and clean up measures to eliminate the breeding places of the pests wherever possible

Repellents and Acaricides

Individuals who must remain exposed to arthropods in infested areas can obtain complete freedom from some species and a high degree of protection from the others by using adequate amounts of the proper repellents applied in the approved manner Some repellents have little or no odor and give protection for two to eight hours when applied to the skin and for several days or weeks when applied to the clothing

True repellents differ from insecticides in that they do not kill the insects but discourage them from biting or landing on treated surfaces The materials recommended for use against chiggers function less as true repellents than as acaricides causing rapid knockdown of the mites before they have a chance to bite They are discussed with the repellents however since their function is the same and since the best repellents are also effective against chiggers (see pp 777–779)

Repellents are marketed commercially as liquids pressurized sprays (aerosols) salves sticks and powders Liquids are usually the most economical but pressurized sprays have the advantage of being convenient

Table XI.10. The Chemical Control of Arthropods of Medical Importance[1]

ARTHROPOD	PLACE OF TREATMENT	CHEMICAL	AMOUNT AND METHOD USED	TOXICITY TO HUMANS*
Mosquito and fly adults.	1 Inclosed spaces as barracks rooms barns airplanes etc.	1 Aerosols† Pyrethrum DDT Aerosol 1% pyrethrines + 2 to 3% DDT + 2% sesame oil in freon	Aerosol bomb—spray 4 sec per 1000 cu ft. Spray into air Spray 2 or 3 times this amount for aircraft disinsectization	None
		2 DDT‡ Spray Residue Deposit a DDT in kerosene (5% DDT in deodorized kerosene) Use technical DDT at rate of 7 oz per gallon of kerosene to make 5% spray	Heavy spray on interior of buildings (1 qt per 250 sq ft) Particular attention to where flies and mosquitoes rest. One application will usually control flies and mosquitoes in treated buildings for 2 3 mo When DDT resistant strains of flies or mosquitoes are encountered sprays containing 0 5 to 1% of dieldrin or lindane may be used effectively If flies and mosquitoes are also resistant to dieldrin and lindane use sprays containing 2% of malathion or 1% of Diazinon	No appreciable toxicity when used properly at recommended dosages. Protect foods dishes, and cutlery
		b DDT water emulsion concentrate	1 part of 25% concentrate to 4 parts of water and use same as in (2) above (Note emulsion conc. should only be used when specifically authorized)	Relatively nontoxic when properly used at recommended dosages
		3 Pyrethrum Extracts (1 lb pyrethrum containing 1% pyrethrines per gallon of kerosene)	100 ml per 1000 cu ft. sprayed into the air as space spray	None.
		4 Pyrethrum plus synthetic organic compounds such as Thanite.	100 ml. per 1000 cu ft spray into the air	None Irritating to some
	2 Outdoors by spraying from airplanes	1 Insecticide Airplane Spray 20% DDT (DDT in fuel oil and auxiliary solvent) or 5 to 10% DDT in fuel oil.	One-tenth to 0 25 lb of DDT per acre will greatly reduce adult mosquito and fly populations and control mosquito larvae for one to two weeks. If resistance to DDT is encountered BHC (40% gamma isomer) may be used at the same rates If the mosquitoes are resistant to BHC also malathion may be used	Nontoxic when used properly at recommended dosages.
	3 In jungle or other vegetated areas.	1 Mist fogs, aerosols etc made from 5 to 10% DDT in kerosene or fuel oil lube oil or a mixture of these or 20% airplane spray as above.	One to two quarts per acre will usually give temporary control Around a clearing apply spray on vegetation in a 50-foot or wider band encircling area to form a barrier with mist blowers fog generators or aerosol generators	Nontoxic when used properly at recommended dosages Avoid prolonged contact.
Mosquito larvae	1 Streams lakes swamps pools, ruts and water-containing receptacles around houses.	1 DDT Oil Solutions (1 5% DDT in kerosene diesel, or fuel oil)	Prepare by adding 2 lbs DDT per 25 gallons of oil Use 5 qts of 1% DDT or 1 qt of 5% DDT per acre of water Apply with a fine spray nozzle with main emphasis where aquatic vegetation is thick particularly along water margins	Avoid prolonged contact.
		2 DDT water Emulsion Concentrate (25% DDT)	Dilute 1 part concentrate with 24 parts water Use 10 qts of dilute spray per acre Emphasis on water margin as above This preparation can be used safely on agricultural crops or other vegetation where oil preparations may cause injury Lasts 7 to 10 days	Nontoxic when used at recommended dosage Avoid prolonged contact

		Insecticide Airplane Spray—5% DDT; DDT in fuel oil and auxiliary solvent	Spray from airplanes. Amount and method as listed above for adults [2]	Same as above.
		4. Fuel oil: light fuel oil or No. 2 grade, kerosene [illegible]	15–25 gal. per acre depending on density of aquatic vegetation. Apply as a spray every 7–10 days	Essentially non-toxic
		5. Paris Green (copper acetoarsenite) containing 50% arsenic oxide	1 lb. Paris green per acre. For hand or power dusting dilute to 5% [illegible] fine sand, [illegible] hydrated lime [illegible]. As an airplane dust dilute to 5%. Apply every 10 days. For control of *Anopheles* mosquitoes only	Very toxic if eaten. Non-toxic in water at recommended dosages.
		6. DDT dusting powder 10% DDT	Dilute 10% powder with several parts of any dry diluent and apply at rate of 0.2 lb. of DDT per acre [illegible] equipment. [illegible] in [illegible] where oil preparations may cause damage	None
		7. Insecticide DDT Wettable powder	Make 2.5% suspension and apply as a spray at the rate of 0.2 lb. of DDT per acre. Keep well agitated	Non-toxic when used as recommended
		8. Dieldrin	1% dieldrin emulsion may be used effectively as a spray to control pests that are resistant to DDT. Apply in a similar manner as for DDT solution above	Slightly toxic [illegible] when used properly at recommended doses
		Lindane or BHC 40% gamma isomer	Same as for dieldrin	Same as above
		9. Parathion	May be applied as solution, emulsion or granules at 0.07 to 0.1 lb. of [illegible] per acre [illegible] by local [illegible]	Highly toxic by contact or ingestion; [illegible] safe only [illegible] experienced operators.
		Malathion	Apply same as parathion above but at rate of 0.1–0.5 lb. per acre	Non-toxic when used as recommended
Fly larvae	1. Latrines	1. Pyrethrum in oil, kerosene, fuel oil or water	Thorough wetting of breeding places 2 or 3 or 4 times weekly by means of [illegible] fly larvae	Essentially non-toxic.
		Lindane or BHC 40% gamma isomer	[illegible] powder [illegible] weekly [illegible] will give good control	Non-toxic when used as directed
	2. Garbage dumps, manure heaps and other breeding places.	Lindane or BHC 40% gamma isomer	Same as above for control in latrines. Note: Continued use of these materials may result in insect resistance	Same as above

[1] Originally prepared by Captain W. N. [illegible], Sanitary Corps. Extensive research on the [illegible] of DDT against insects affecting man and animals has been done by the Orlando Laboratory, Bureau of Entomology and Plant Quarantine, United States Department of Agriculture.

[2] United States Department of Agriculture [illegible]. See Patent by Goodhue and Sullivan.

[3] DDT in an aerosol [illegible] for [illegible].

[4] See Table XI [illegible] for further details [illegible].

Table XI.10. The Chemical Control of Arthropods of Medical Importance[1]

ARTHROPOD	PLACE OF TREATMENT	CHEMICAL	AMOUNT AND METHOD USED	TOXICITY TO HUMANS*
Mosquito and fly adults	1 Inclosed spaces as barracks rooms barns airplanes etc.	1 Aerosols† Pyrethrum DDT Aerosol 1% pyrethrines + 2 to 3% DDT + 2% sesame oil in freon.	Aerosol bomb—spray 4 sec per 1000 cu ft. Spray into air. Spray 2 or 3 times this amount for aircraft disinsectization	None.
		2 DDT‡ Spray Residue Deposit a DDT in kerosene (5% DDT in deodorized kerosene). Use technical DDT at rate of 7 oz per gallon of kerosene to make 5% spray	Heavy spray on interior of buildings (1 qt per 250 sq ft). Particular attention to where flies and mosquitoes rest. One application will usually control flies and mosquitoes in treated buildings for 2-3 mo. When DDT resistant strains of flies or mosquitoes are encountered sprays containing 0.5 to 1% of dieldrin or lindane may be used effectively. If flies and mosquitoes are also resistant to dieldrin and lindane use sprays containing 2% of malathion or 1% of Diazinon	No appreciable toxicity when used properly at recommended dosages. Protect foods, dishes, and cutlery
		b DDT water emulsion concentrate	1 part of 25% concentrate to 4 parts of water and use same as in (2) above (Note emulsion conc. *should only be used when* specifically authorized.)	Relatively nontoxic when properly used at recommended dosages
		3 Pyrethrum Extracts (1 lb pyrethrum, containing 1% Pyrethrines per gallon of kerosene)	100 ml per 1000 cu ft sprayed into the air as space spray	None.
		4 Pyrethrum plus synthetic organic compounds such as Thanite.	100 ml per 1000 cu ft spray into the air	None. Irritating to some
	2 Outdoors by spraying from airplanes.	1 Insecticide Airplane Spray 20% DDT (DDT in fuel oil and auxiliary solvent) or 5 to 10% DDT in fuel *oil*	One-tenth to 0.25 lb of DDT per acre will greatly reduce adult mosquito and fly populations and control mosquito *larvae for* one to two weeks. If resistance to DDT is encountered BHC (40% gamma isomer) may be used at the same rates. If the mosquitoes are resistant to BHC also malathion may be used	Nontoxic when used properly at recommended dosages.
	3 In jungle or other vegetated areas.	1 Mists, fogs, aerosols etc. made from 5 to 10% DDT in kerosene or fuel oil, lub oil or a mixture *of these or 20%* airplane spray as above	One to two quarts per acre will usually give temporary control. Around a clearing apply spray on *vegetation* in a *50-foot* or wider band encircling area to form a barrier with mist blowers, fog generators or aerosol generators.	Nontoxic when used properly at recommended dosages. Avoid prolonged contact.
Mosquito larvae	1 Streams, lakes swamps pools rain and water containing receptacles around houses.	1 DDT Oil Solutions (1.5% DDT in kerosene, diesel, or fuel oil)	Prepare by adding 2 lbs DDT per 25 gallons of oil. Use 5 qts of 1% DDT or 1 qt of 5% DDT per acre of water. Apply with a fine spray nozzle with main *emphasis where* aquatic vegetation is thick particularly along water margins	Avoid prolonged contact.
		2 DDT-water Emulsion Concentrate (25% DDT)	Dilute 1 part concentrate with 24 parts water. Use 10 qts. of diluted spray per acre. Emphasis on water margin as above. This preparation can be used safely on agricultural crops or other vegetation where oil preparations may cause *injury. Lasts 7 to* 10 days	Nontoxic when used at recommended dosage. Avoid prolonged contact.

		3 Insec d A rplane Spray 20% DDT DDT n tuel o and a x l ry u enus	Spray from a rplanes. Amount and me hod as s ed abo e for adul s 2	Same as above
		4 Pe roleum Oil L gh fuel o l of No 2 grade or l unke L d lu d 4 w h kerosene	15 25 gal ons per acre depend ng on dens y of aqua c vege a tion Apply as a spray e ery 7 0 days.	Essen ally non- ox c
		5 P s Green Copper ace oa en e on a n ng 50% p us of arsen ous ox de)	r per acre F r hand or power dus ng d lu e to ne t du s uch as road dust fine sand a c hy cond oned flour As an a rplane du d lu e to every 1 10 days F r con ol of An phele mos-	Very tox c if ea en Non oxic n wa er a ecommended dosages.
		6 DDT dus ng powder 10 DDT	wder w h several p cts f any dry d s d l ent and of 0 2 lb of DDT per acre w h ro ary dus er b e equ pmen Th s ma e al may be used safely where o l prep ra ons may cause damage	None
		7 Insec d DDT Wa er d pers b e Powder	pens on and pply as o a he ra e f 0 2 lb cre Keep well ag a ed	Non ox c when used as recom mended
		8 D eld n	er em on may be used effe cly a a p ay cies ha are res art to DDT Apply n s m lar DDT o l solu on abo e	S ud es nd a e non ox c ty when used properly a recom mended doses.
		9 l ndane o BHC 40% y some	eldrin	S me as above
		10 Para h on	l as oil solution em l on or granules a 0 0? to a h on p a re o con ol larvae re s an o all yd oca bons	H ghly ox c by con act or n ges on but safe o use as d rected by exper nced opera ors.
		M la hion	para h or bo c bu a a es of 0 1 o 0 5 lb	Non ox when sed as recom mended
Fly larvae	1 La nes.	Pe role m O ls ke osene fuel o wa e mo or o e c	ng he en e su face of he b eed ng me l a 3 or v by means of a o rse p a w ll on rol mos	Essentially non ox c
		2 L ndane BHC 40% y somer	s on or wettable powder of e her of these chems w ce week y as we sp ay o er he en e s rfa e of med a w ll g ve good con rol	Non oxic when used as d rec ed
	2 Ga b ge d mps, r bb h heaps, nd o her breed ng p a es	1 Lin l ne or BHC 40% y some	or con ol n la r nea No e Con nued use of ls may resul n nsec ic de res s ant stra ns.	Same as above

[1] Origina ly p epared by Cap a n W N So an Sn C Ex ensive research n he Un ed S a es on I e b ng e effec s of DDT g ns nsec s affec ng man and an mals has been done by he O lando Labora ory Bu e u of En omology and Plan Quarantine Un ed S a es Dep tment of Agr culture.

† Un ed States Depar men of Agr cul ure Public Ser ce Pa en by Goodhue and S van

‡ DDT s an abbrev a on for d c loro-d pl enyl t chloroe l ane

* See Table XI 11 for fur her detailed nforma ion on oxic y

Table XI 10 The Chemical Control of Arthropods of Medical Importance (Continued)

ARTHROPOD	PLACE OF TREATMENT	CHEMICAL	AMOUNT AND METHOD USED	TOXICITY TO HUMANS
	3 All larval breeding sites.	1 Malathion or Diazinon	Where fly larvae are resistant to chlorinated hydrocarbons use Diazinon or malathion at 100 to 200 mgm. per sq ft of breeding surface in solutions, emulsions dusts, or granules	Non toxic when used as recommended
		2 Parathion	Same as above	Toxic but safe if used carefully as directed
Lice (cootie grey back) *Pediculus humanus* var *humanus* and *ap* pub c louse (crab) *Phthirus pubis*	1 On body and clothing	1 DDT Powder (10% DDT in pyrophyllite or other inert dusts)	Mass Treatment Thoroughly dust between inside garment and skin self by applying dust gun at all openings of clothing. Use 1.5 ounces per individual. Body lice are most frequently found in the seams of clothing	Essentially non toxic
			Individual Treatment Apply powder from sifter top can over the entire inner surface of underwear and treat seams on the inside of shirt and trousers use one (1) ounce of powder	
		2 Lindane dust (1% in inert dust)	Should be applied as described for DDT above Three applications are recommended Note Not more than 60 gm per application per person and applications not closer than 7 days apart Particularly recommended where DDT resistant lice are encountered	Studies indicate non toxicity when used properly at recommended dosages.
	2 Body	1 Insecticide Spray Delousing (DDT, benzyl benzoate, benzocaine and emulsifier)	Dilute concentrate 1 part with 5 parts of water and spray hairy parts of body with about 20 to 30 ml. of the liquid	Essentially non toxic. Protect eyes during application.
	3 Clothing impregnation.	1 DDT Water Emulsion Concentrate	Dilute to 2% DDT Use ordinary laundry facilities. 1 pt per set of underwear	Studies indicate non toxicity when used properly at recommended dosages.
	4 Mass clothing treatment	1 Methyl Bromide (danger)	8 lbs. per 1000 cu ft for half hour Use in specially constructed fumigators. To be used by experts only Individual clothing and equipment fumigation may be done in special rubberized bags by breaking an ampule of methyl bromide in bag	Very toxic No warning odor Safe dosage 30 parts per million for operators
Fleas *Xenopsylla* spp *Nosopsyllus* spp *Pulex* ... *ans* etc.	1 Rooms.	1 DDT Oil Solution (5% DDT in kerosene)	1 gal 5% DDT in oil per 1000 sq ft. will give good results. 2 lbs. DDT in 5 gallons oil	Non toxic at recommended dosages.
		2. Chlordane oil solution (2%)	1 gallon per 1000 sq ft as coarse wet spray	Same as above
		3 Malathion oil solution (2 to 3%)	Same as above for control of fleas resistant to chlorinated hydrocarbons	Same as above
		4 Diazinon oil solution 0.5%)	Same as above	Same as above
		5 Lindane Dust (1% in any inert diluent dust)	Dust lightly over floor and furniture with hand or rotary type duster	Same as above

		6 Insecticide Dust Pyrethrum and/or Synthetics	Same as No 5 above	Same as above
		7 DDT Dust (10% in pyrophyllite)	Same as for Lindane dust No 5 above	Nontoxic if used as recommended
		8 Naphthalene (moth flakes)	3 lbs per 1000 cu ft Thorough dusting on floor especially cracks. Overnight fumigation	Nontoxic unless eaten.
		9 Paradichlorobenzene	Same as No 5 above	Same as above
	2 Animals	1 DDT Dust (10% in pyrophyllite)	Light application over animal Rub lightly into hair	Slightly toxic to cats and other animals that lick themselves
		2 Rotenone Dusts (Derris powders)	Thorough application over animal Rub lightly into hair	None
		3 Malathion powder (4%)	Same as No 1 above	Nontoxic when used as directed
	3 Rat runways rodent burrows rubbish heaps and other rodent and flea infested areas	1 DDT Dust (10% in pyrophyllite)	Dust lightly over entire area to kill fleas leaving rodents. Dust heavily in burrows and runways to kill fleas on rodents going through the dusted area	None if used as recommended
Bedbugs (Cimex spp)	1 Enclosed spaces	1 DDT Kerosene Solution (5% DDT in kerosene)	1 qt sprays 5 beds and mattresses. Thoroughly spray mattresses beds and into cracks and crevices in wall with particular attention to springs and the corners of beds. Residual effect of a year or more	Studies indicate nontoxicity when used properly at recommended dosages
		2 Lindane oil solution 0 1%	Apply lightly to mattresses and furniture thoroughly into cracks and crevices in wall. Do not treat bedding of infants. Use to control DDT resistant bugs	Safe when used as directed
		3 Malathion oil solution (1%)	Same as above	Nontoxic when used as directed
		4 Hydrogen Cyanide Danger	To be used by experts only	Extremely toxic
		5 Pyrethrum extract 1 lb per gallon of kerosene	Thorough wetting of cracks and crevices containing bedbugs. Four monthly treatments. Repeat	None
Roaches	1 Enclosed spaces	1 Chlordane (2%) and DDT (5%) in kerosene	Apply as wet spray directly to cracks, crevices and behind objects particularly in kitchens, bathrooms and near water supplies. Also very effective against ants	Toxic. Should be used according to recommendations. Protect foods and utensils.
		2 Malathion (2 to 3%) in oil solution or emulsion sprays	Same as above. Use to control roaches resistant to chlorinated hydrocarbons	Nontoxic when used as directed
		3 Diazinon (0 5%) in solution or emulsion sprays	Same as above	Same as above.
		4 Chlordane (5% to 10% dust)	Thorough application to cracks, crevices, and all infested areas. Also very effective against ants.	Toxic. Protect food and utensils.

Table XI 10 The Chemical Control of Arthropods of Medical Importance (Continued)

ARTHROPOD	PLACE OF TREATMENT	CHEMICAL	AMOUNT AND METHOD USED	TOXICITY TO HUMANS
Roaches (cont'd)		5 Sodium Fluoride Dust (should be colored)	Thorough application to racks, crevices and all infested areas. Keep dry	Very toxic if eaten
Mites (Chiggers, red bugs, harvest mites *Eutrombicula* spp (larvae)	1 Clothing	1 Dimethyl phthalate, benzyl benzoate or diethyl toluamide	Barrier Treatment Apply thin layer ½ in wide along all openings of uniform and socks. Good until uniform is washed. Most rapid acting	Nontoxic
	2 Clothing impregnation	1 Dimethyl phthalate emulsion (90% DMP and 10% emulsifier)	Clothing impregnation with 5% DMP emulsion in water gives excellent protection until clothes are washed. Mix 1 gal of 90% emulsion conc with 17 gal. water. Will treat 35 to 50 fatigue suits and socks. Wring out thoroughly and dry before wearing	Nontoxic
		2 Dimethyl phthalate solution (5% in volatile solvent)	Impregnate clothing with 5% solution of DMP in volatile solvent such as dry cleaning fluid 3 to 3½ pints for socks, trousers and jacket.	Nontoxic (except for solvent)
		3 Diethyl toluamide 5% emulsion or solution	Same as No 1 or No 2 above	Nontoxic.
		4 Benzyl benzoate 5% solution or emulsion.	Same as No 1 or No 2 above. Effective after 2 or 3 washings	Nontoxic when used as directed; do not apply to skin
	3 Infested outdoor areas.	1 *Dieldrin* spray or dust.	Treat ground and low vegetation over entire infested area with 2 lbs of dieldrin per acre in spray (emulsion or wettable powder) or dust	Nontoxic when used as directed
		2 Chlordane spray or dust	Same as above	Same as above
		3 BHC (40% γ isomer) spray or dust	Same as above	Same as above
Scabies mange (*Sarcoptes scabiei*)	1 Body	1 Insecticide Spray Delousing (DDT benzyl benzoate benzocaine and emulsifier)	Dilute 1 part concentrate and 5 parts water. Apply as spray or by hand over body except head. Plain benzyl benzoate at 25% dilution in alcohol is also effective, used same as above.	Nontoxic when used as recommended
		2 Eurax Cream or Kwell ointment	Thorough application to affected parts	Nonirritating
Ticks (most species)	1 Animals.	1 Toxaphene (0.5% emulsion in water)	Apply thoroughly as a spray to all parts of animal's body. Do not dip animals in this preparation	Safe if used as recommended. Do not use on dogs.
		2 Lindane-DDT (0.025% lindane and 0.5% DDT) emulsion in water	Same as for toxaphene above.	Safe as recommended
	2 Infested areas	1 DDT D	Use 4 lbs of DDT diluted with seven parts of inert diluent. Spread thoroughly over infested areas. Will give fair control for 1 season.	Nontoxic

		2 DDT sp ay	Use 2 o 4 lbs. of DDT per a re as an emulsion o we ble powd r spray Apply o g ound and low egeta on G es good con ol for one season	Nontox c
		3 D eldrin Dus	Use 0 5 to 1 0 lbs of dieldr n d lu ed wi h several pa ts of nert d l en per acre dusted horoughly over all nfes ed areas W ll g e good con rol for one season	Non ox c when used as d ec ed at recommended doses.
	3 Clothing m- pregna on	1 M 1960 (Prepa a on con a n ng 3 par s of 2 bu yl 2-ethyl 1 3 p opane tol N bu ylace amide and ben yl benzoate and 1 part of an emu si er)	Uniform and socks should be d pped n emulsion so as o evenly d s bute about 3 oz of the chemica s on the garments. W ll g ve excellent p o ection o the wearer against t ks and ch g- gers for about 2 weeks, or un l clo h ng s laundered	S ud es ind ca e non o ic y when used *properly at recommended* dosages Not recommended for direct appl ca on o sk n r for general c l an use
		2 D e h l ol tam de 5% emulsion or solu- on	*Impregna e clo hing as d rec ed for m es*	Non oxic
		3 Inda one	Same as abo e	Non oxic
orp ons	1 Rooms	1 DDT 5% sol tion or em l on sprays	App y o ndoor hid ng places f nd oor nfes a ons are heavy Re move or spray rash p les and ot er outdoor h d ng places near wastes	Non ox c when used as d rected
		2 Ch o dane 2% solutions r emulsion prays	Same as above	Same as abo e
		3 D eldr n 0 5 of on or em u sion sprays	abo e	Same as above
lack W l w sp ders	1 Houses	1 DDT hlordane or d eldr n sp ays.	r scorp ons	Same as abo e
	2 Pr es	DDT o chlord ne sprays	y applica ions of spra s con ain ng 5% DDT or 2% c o wa ls and espec a y under sea s Sol t on em l we able powders may be used	Same as abo e
eduvid e	1 Hou es	1 D eldrin spray	ed areas of I o ses w h 125 mgm of d eldrin per sq sol on o emuls on sprays El mina e b eed ng pla es	Same as abo e
		2 Lindane spray	bove w h 50 mgm per sq f	Same as above
re an s	1 Infes ed yards	1 Hep achlor em l on sp ay or gran e	re nfes ed area a a e f lb l ep l or per a re n of nests a one s unsa fac ory	Same as above
		D eld n en on spray or g anu es	bove	Same as o e
leuli e adults	1 Infested outdoor areas,	1 DDT l ndane or mala on sprays, fogs or mokes	d rec ed for control of ad n osqu oes.	S me as above
leuli e larvae	1 S t marshes	1 D ldrin g an les	ldr n a 1 lb per acre n granular formula ns	Sam e as above
mul dae ad l s	1 Infes ed ou door a e s	1 DDT s l tion sprays	T (5% o 10% n fuel oil a 0 4 lb DDT per a e w h r a r eq pment	S me as above

Table XI.10. The Chemical Control of Arthropods of Medical Importance (Continued)

ARTHROPOD	PLACE OF TREATMENT	CHEMICAL	AMOUNT AND METHOD USED	TOXICITY TO HUMANS
Simuliidae larvae.	1 Streams.	1 DDT sprays.	Apply DDT with ground or air equipment as solution, emulsion or wettable powder spray. Apply 0.1 ppm. (based on volume of stream) for 15 minutes at stream intervals of 1 mile or at 0.05 lb. per acre of water surface.	Same as above.
Psychodidae adults.	1 Houses and outdoor harborages.	1 DDT residual sprays.	Apply DDT solution, emulsion or wettable powder sprays to interiors of houses and outdoor resting places such as stone walls, at 100–300 mgm. of DDT per sq. ft.	Same as above.
		2 Lindane residual sprays.	Apply lindane as above at 25 mgm. per sq. ft. Residual period is shorter than with DDT.	Same as above.
Tabanidae adults.	1 Infested areas.	1 DDT sprays.	In limited areas some control of tabanids has been obtained with DDT applied as recommended for control of adult mosquitoes but in general control measures are unsatisfactory.	Same as above
Chloropidae adults.	1 Infested areas.	1 DDT, lindane or malathion sprays.	Temporary control of adults may be obtained by using DDT, lindane or malathion as sprays, mists, or fogs, as recommended for control of adult mosquitoes and flies.	Same as above.
Glossina.	1 Infested stream banks.	1 DDT residual emulsion spray.	Apply 5% DDT emulsion spray at 18 gallons per mile every 2 weeks (4 times a season).	Same as above
		2 Dieldrin residual emulsion spray.	Apply 5% dieldrin emulsion spray as above once a season.	Same as above.
	1 Generally infested unforested areas.	1 DDT aerosols or mist sprays.	Apply fine mist or smoke aerosols (5 to 50 microns) by air at 0.1 to 0.2 lbs. of DDT per acre (e.g.) 1 qt. of 10% oil solution).	Same as above.
			INSECT REPELLENTS	
Repellents for flies, mosquitoes, gnats, mites, blackflies, sandflies, fleas, and possibly others.[3]	1 Exposed surfaces of body and clothes.	1 Diethyl toluamide.	*Application on Skin.* Shake ½ teaspoonful into palm of hand, rub hands together and then apply in thin layer to face, neck, ears, hands and wrists. Do not get in eyes and mouth.	Nontoxic. Very irritating to the eyes.
			On clothes. Spray or apply by hands on clothes. Effective for a number of days. Best all around repellent.	
		2 Dimethyl phthalate.	Particularly effective against *Anopheles* and larval mites (chiggers). Use same as (1) above.	Same as above.
		3 Indalone.	Same as (1) above. Best use against biting flies.	Same as above.
		4 2-ethyl hexanediol 1, 3 (repellent 612).	Same as (1) above. Particularly effective against *Aedes*.	Same as above

[3] See pp. 777 (clothing impregnation) and 779 for tick repellents.

Mosquito and Biting Fly Repellents Experiments against various species of mosquitoes and biting flies from Panama to Alaska have shown diethyltoluamide to be outstanding as an all purpose repellent for application to the skin Chlorodiethylbenzamide is also highly effective against a wide range of species and ethyl hexanediol dimethyl carbate dimethyl phthalate and indalone are all good general repellents that are outstanding against certain species

Repellents suitable for application to the clothing are required by troops or others exposed to heavy mosquito infestations since mosquitoes easily bite through untreated clothing of normal weight The use of clothing treatments does not eliminate the need for skin applications however All the repellents mentioned in Table XI 10 may be used on clothing but some of the best clothing treatments are not recommended for skin applications The most effective repellents recommended for
'' tyl ethyl propanediol
The present military
') is effective against

Application to Clothing A simple method of applying a repellent to clothing is to shake about a dozen drops into one hand rub the hands together and rub lightly on the parts of the socks shirt or trousers that fit tightly and where bites occur This procedure is repeated until the areas to be treated have been covered If preferred a light spray may

Use against Chiggers For protection against chiggers (red bugs) the materials should be applied to the clothing rather than to the skin A treatment of clothing with any of the mosquito repellents will remain effective for several weeks unless the clothing is washed or soaked in water Benzyl benzoate will also protect against chiggers and will remain effective in clothing after two launderings Benzyl benzoate may be injurious at high dosages the recommended dosage should not be exceeded and it should not be used on the skin M 1960 is still effective after one or two washings

The simplest way to treat clothing is to apply a spray However if a bottled repellent is used liberal applications are made by hand along all openings of the clothing such as inside the neck band the fly and cuffs of trousers and the tops of socks Benzyl benzoate should not be applied by this method

Impregnation Method The best method of obtaining complete protection under all conditions of exposure is to impregnate all the outer

is preferable for this purpose as it is more resistant to leaching by water

In the solution method, the repellent is dissolved in enough dry-cleaning fluid or other volatile solvent to wet the garment thoroughly without leaving any excess About 3 pints are required for an outfit of heavy cotton cloth After all parts of the garment have been saturated with the solution, the cleaning fluid is allowed to evaporate

An emulsion can be made by mixing 2½ ounces (5 tablespoonfuls) of the repellent with 3 pints of water and ¼ ounce (1½ teaspoonfuls) of an emulsifier or 1 ounce (2 tablespoonfuls) of soap All parts of the garments should be saturated with the emulsion, wrung lightly and dried thoroughly before wearing

Barrier Method Considerable protection will be obtained by treating only the openings of the clothes—inside the neck band, fly and cuffs of shirts, inside the waist band, fly and cuffs of trousers, on the socks, both above the shoes and inside the shoe below the tongue The material is applied by daubing, spraying or drawing the mouth of the bottle along the cloth to make a band ½ inch wide Women's clothing may be protected in the same general way

Flea Repellents. Diethyltoluamide is a superior flea repellent, par-

... garments ... the main ...

and legs of trousers Undecylenic (undecenoic) acid, *N* propylacetanilide, benzyl benzoate and M-1960 are also good flea repellents, treatment with them remains effective through several days of ordinary wear

Tick Repellents. None of the repellents mentioned above will provide complete protection against ticks, but several will afford a high degree of protection against one of the most annoying species, the lone star tick (*Amblyomma americanum*). The socks and all the outer clothing should be treated by spraying or by the impregnation method described for use against chiggers M-1960 is the most effective repellent for use against ticks, but it is not recommended for general civilian use Other repellents, in order of preference, are *diethyltoluamide, indalone,*

... ted cloth-

wear

Precautions. The repellents discussed here have been found safe for use as recommended Most are toxic if taken internally Some people may be allergic to them and will show a rash or other minor *skin reaction*

... mbranes

... 50 per

some

plastics to varying degrees They will damage a few types of synthetic cloth (for example, acetate rayon but not nylon), fingernail polish, and articles that are painted, varnished or made of certain plastics Ethyl hexanediol has the least injurious effect, and diethyltoluamide is less injurious than the other materials

76

Toxicology of Pesticides

Charles S Petty

Health Hazards

Health hazards associated with the large scale use of any chemical agent are extremely hard to define with accuracy This is particularly true in the case of the so called economic poisons chemicals used in the control of crop insect pests and destructive rodents These agents are employed outside of industrial control and in huge quantities by large numbers of persons in all areas of the United States Indeed their use throughout the world is becoming commonplace as increasing emphasis is placed upon insect and rodent disease vectors Medical surveillance is not available to many of those having intimate contact with these economic poisons *At least* 100 to 200 accidental deaths due to poisoning by pesticides are recognized each year in the United States It is impossible to estimate the number of deaths due to similar unrecognized poisonings

The morbidity as a result of occupational and accidental exposure to these poisons is a completely uncharted area In California in 1955 pesticides accounted for 8 per cent of all agricultural injuries and nearly 2 per cent of the total work injuries Little other accurate data are available Many instances of sublethal poisoning by economic poisons must take place each year

Because of the relative unfamiliarity of medical practitioners with poisonings in general and with poisonings by pesticides in particular many cases are improperly diagnosed and treated Another difficult problem is posed by the multiple trade names under which many of the toxic pesticides are marketed One handbook lists more than 6000 trade names of pesticides

In dealing with pesticide poisoning it must be remembered that the toxic agent will usually be diluted or placed in solution with a second compound The diluent or solvent may also be toxic Xylene and kerosene are commonly employed in this manner In some cases it may be impossible to determine whether the pesticide or the diluent or both are responsible for the clinical picture of poisoning Some pesticides have been considered *to have caused skin reactions when actually the diluent was* responsible for the local symptoms

The possibility of pesticide mixtures being employed must also be kept in mind Exposed individuals often do not realize that the pesticide they use has more than one toxic ingredient in addition to a solvent or diluent that may also be toxic

Pesticide Classification

Most pesticides used in the United States may be categorized as fol lows

- I Insecticides
  - A Chlorinated hydrocarbons
  - B Organic phosphates
  - C Inorganic chemicals
  - D Dinitrophenols
  - E *Hydrocarbon solvents*
  - F Vegetable products
- II Rodenticides
  - A *Inorganic chemicals*
  - B Plant alkaloids
  - C ANTU
  - D Warfarin

Two groups of these agents the chlorinated hydrocarbons and the organic phosphates deserve special recognition and discussion because of their widespread use and unique toxicologic properties

Chlorinated Hydrocarbon Insecticides

The prototype of this class is DDT (chlorophenothane dichloro diphenyl trichloroethane) It has been used in larger quantity and much more widely than any other member of this group Others are

Benzene hexachloride (BHC)
Chlordane
Lindane
Aldrin dieldrin and endrin
Toxaphene

All of the chlorinated hydrocarbon insecticides are relatively stable compounds Some are stable enough to be stored in human fat in the active form others as degradation products This property may be re sponsible for a type of dieldrin poisoning described below The acute toxicity in man is essentially the same [illegible] hydro carbons All of them may be absorbed [illegible] by the gastrointestinal and respiratory [illegible] nism of action is not known these chemicals stimulate the central nervous system Therefore the usual signs and symptoms of intoxication include irritability hyperexcitability and tonic clonic convulsions followed by depression and death

There is no specific antidote for poisoning by the chlorinated hydro carbons The therapeutic objectives are to control the hyperactive cen tral nervous system with sedatives and to remove the unabsorbed poison from the stomach or skin The drug of choice is pentobarbital because of its rapidity of action and universal availability Doses necessary to achieve sedation and calmness without sleep may appear unusually large and may be of such magnitude that anesthesia would be induced if the subject had not previously been poisoned Supportive therapy in the form of oxygen administration and artificial respiration may also be re quired No permanent residua are to be expected if the victim survives the acute phase of poisoning

In general the potential chronic toxicity of these insecticides has never

been conclusively demonstrated However recently a form of chronic poisoning among workers exposed to dieldrin over a prolonged period has been recognized The symptoms which characterize the mildest form of poisoning with dieldrin include headache (often not responsive to drugs) malaise insomnia and bad dreams blurring of vision giddiness slight involuntary muscular movements and other mild symptoms A more severe form of intoxication may

an au

lowing contact with dieldrin improvement is the rule However weeks afterward recurrence of the convulsive episodes may be noted

Organic Phosphate Insecticides

These agents vary markedly in their toxicity to man Some are of such extreme toxicity that respirators and protective clothing must be worn by those dealing with them Others are relatively innocuous and ingestion of a large quantity might be necessary to produce poisoning in man

New members of this group are constantly being developed At this time the most widely employed of the organic phosphates are

Parathion
Methyl parathion
Tetraethylpyrophosphate
Guthion
Malathion
Diazinon
Systox

All of the organic phosphate insecticides can be absorbed through the intact skin and the respiratory and gastrointestinal systems The symptoms of poisoning are similar with all members of this group Mild intoxication is characterized by profuse sweating and salivation narrowed pupils difficulty in breathing headache poor visual accommodation and abdominal cramping The symptoms and signs of more severe poisoning may include diarrhea involuntary urination marked weakness and muscular fasciculations Very severe organic phosphate poisoning is marked by coma convulsions and death h

symp

o

a

to

o

N organic phosph

sec Most of the

from in

organic poisoning is

survive chronic poisoning has not been encountered although

Table XI.11. Essential Information on Some Important Economic Poisons (Insecticides and Rodenticides)

NAME	TYPE	SYNONYMS	LOCAL ACTION	SYMPTOMS OF POISONING	FATAL PERIOD	FATAL DOSE	TREATMENT FOR POISONING
ALDRIN (Hexachlorohexahydro-endo exo-dimethanonaphthalene) (Chemically closely related to dieldrin)	Insecticide Chlorinated hydrocarbon group	HHDN	None Absorbed through intact skin.	See dieldrin. Anorexia may be marked	See dieldrin.	Moderately toxic Not determined Severe symptoms from 25 mgm./kg	See dieldrin.
ANTU (alpha naphthyl thiourea)	Rodenticide.	Ant rat Bantu, Rattrack	None Not absorbed through intact skin.	Mild gastrointestinal upset Emesis which usually protects patient	Unknown.	Slightly toxic Estimated 1 gm.	No specific antidote Gastric lavage. Symptomatic treatment
*ARSENIC (Used as Calcium arsenite and Calcium trioxide)	Insecticide Insecticide pesticide.	Tricalcium arsenate Kalo White arsenic, arsenious oxide.	Mild dermal irritation.	Gastroenteritis dermatitis headache lethargy visual disturbances, muscular weakness, collapse.	Variable Both acute and chronic toxicity	Highly toxic, 0 2 0 5 gm	BAL (dimercaprol) 3 to 4 mg./kg every 6 hrs for the first day and twice daily for a total of 10 days. Gastric lavage catharsis.
BENZENE HEXACHLORIDE (1 2 3 4 5 6 hexachlorocyclohexane)	Insecticide Chlorinated hydrocarbon group	BHC, gammexane. Many trade names.	Skin irritation. Absorbed through intact skin.	Hyperirritability hyperexcitability convulsions. Several isomers of benzene hexachloride are known. Alpha and gamma isomers produce CNS excitation Beta isomer is nontoxic. Delta isomer is CNS depressant	Symptoms develop in 1 to 2 hours. Death in 24 hours	Moderately toxic. About 400 mgm./kg of commercial material	No specific antidote. Gastric lavage Removal of material from skin. Control of CNS hyperactivity with pentobarbital Patient may require large doses of the barbiturate The use of stimulants is dangerous. Calcium gluconate 10% 10 ml I V in addition to above
*CHLORDANE (Octachloromethano tetrahydroindane)	Insecticide Chlorinated hydrocarbon group	Chlordan, 1068 Octachlor Many trade names	A skin irritant when in high concentration. Absorbed through the intact skin.	Early irritability of CNS followed by convulsions and then depression with death due to respiratory failure	Symptoms develop in 30 minutes to 6 hours. Death in several hours to several days	Moderately toxic 6 to 60 gm	No specific antidote Gastric lavage and removal of the material from the skin Control CNS hyperactivity with pentobarbital Avoid oil laxatives Calcium gluconate 10%, 10 ml. I V in addition to above
CHLORTHION (0 0-dimethyl 0-3-chloro-4-nitrophenyl thiophosphate)	Insecticide. Organic phosphate group	Bayer 22/190.	None Absorbed relatively poorly through the intact skin	See Parathion	Not known.	Moderately toxic Not known much less toxic than Parathion.	See Parathion
*DDT (Chlorophenothane Also termed Dichloro-diphenyl trichloroethane)	Insecticide Chlorinated hydrocarbon group	Dicophane	Innocuous as a solid Solutions constitute a hazard through multiple exposures. Rarely skin irritation.	Incoordination muscular twitching spastic paralysis of the legs and convulsions which increase in frequency and severity Eventual depression respiratory failure and death	Symptoms develop in several hours Death as early as 6 hours, some may be delayed for several days	Slightly toxic 500 mgm./kg is marked as fatal oral dose	No specific antidote Gastric lavage. Control convulsions with pentobarbital Large doses may be necessary Calcium gluconate 10% 10 ml I V in addition to above.

DIAZINON (0, 0-diethyl 0-(2 isopropyl 6-methyl 4-pyrimidinyl) thiophosphate)	Insecticide Organic phosphate group	G-24480	None. May penetrate intact skin.	See Parathion.	Probably several hours.	Moderately toxic. Not known Less toxic than Parathion.	See Parathion.
*DIELDRIN (1, 2, 3, 4, 10, 10-hexachloro-6, 7-epoxy-1, 4, 4a, 5, 6, 7, 8, 8a-octahydro-1, 4 endo, exo-5, 8-dimethanonaphthalene)	Insecticide Chlorinated hydrocarbon group	Compound 497, Octalox, Endrin (stereoisomer of dieldrin)	None Absorbed through the intact skin.	Hyperexcitability, tremors ataxia and convulsions followed by CNS depression and death in respiratory failure	30 minutes to 6 hours for onset of symptoms Time to death not well established	Moderately toxic Not determined 10 mgm./kg causes acute illness	See Benzene hexachloride
DILAN (Mixture of Prolan and Bulan)	Insecticide Chlorinated hydrocarbon group	Prolan-Bulan mixture CS 545 A.	None	Not reported in man Would probably resemble those of others of the chlorinated hydrocarbon group	Not known	Slightly toxic Not known	See Chlordane
*DINITROPHENOLS (Several used Dinitrophenol 2, 4 dinitrophenol Dinitrocresol 4 6-dinitro-0-cresol)	Insecticides	DNP DNOC	May cause skin burns (DNOC) Absorbed through intact skin (DNOC)	High fever prostration thirst nausea restlessness flushed skin, deep and rapid respiration, collapse	Hours to days	Highly toxic 30 to 50 mgm./kg	No specific antidote Gastric lavage, emesis, catharsis, cleansing of skin. Cooling of body and maintaining electrolyte balance are extremely important
GUTHION (0 0-dimethyl S-(4-oxo-1, 2, 3-benzotriazinyl 3-methyl) phosphorodithioate)	Insecticide Organic phosphate group	Bayer 17147	None May penetrate intact skin	See Parathion	Probably several hours	Moderately toxic Not known Less toxic than parathion.	See Parathion
HEPTACHLOR (one of active compounds in technical chlordane)	Insecticide Chlorinated hydrocarbon group	See Chlordane	See Chlordane	See Chlordane	See Chlordane.	See Chlordane.	See Chlordane
*KEROSENE (Petroleum distillate Temperature range 204 to 315° C.)	Insecticide Solvent and diluent	Coal oil Deobase is a highly refined and deodorized form	May cause maculopapular eruption of skin	Ingestion results in gagging and coughing with aspiration of the kerosene, followed by depression and bronchopneumonia. Use of kerosene sprays in poorly ventilated areas may lead to headache blurred vision dizziness, unsteady gait nausea, collapse, twitching and coma	Variable	Moderately toxic 30 ml. ingested has caused death. Survival possible with much larger doses.	No specific antidote. Gastric lavage, taking care to avoid aspiration Saline laxative Avoid emesis.
*LINDANE (gamma isomer of benzene hexachloride)	Insecticide Chlorinated hydrocarbon group	Gamkil Hi-Gam Lindex, Lindust, Lincide	See Benzene hexachloride	See Benzene hexachloride	See Benzene hexachloride	Moderately toxic 100 mgm./kg The most toxic of all isomers of benzene hexachloride	See Benzene hexachloride

* Fatal poisoning attributed to this particular agent

Table XI.11. Essential Information on Some Important Economic Poisons (Insecticides and Rodenticides) (Continued)

NAME	TYPE	SYNONYMS	LOCAL ACTION	SYMPTOMS OF POISONING	FATAL PERIOD	FATAL DOSE	TREATMENT FOR POISONING
*MALATHION (0 0-dimethyl S (1 2 dicarboxyethyl) dithiophosphate)	Insecticide Organic phosphate group	4049 Malathion.	None May penetrate intact skin	See Parathion.	Probably several hours.	Slightly toxic Probably 1 to 5 gm	See Parathion
* METHYL PARATHION (Dimethyl p-nitrophenyl thiophosphate)	Insecticide Organic phosphate group	None	None Absorbed through intact skin	See Parathion	Minutes to hours	Moderately toxic Not known less toxic than Parathion.	See Parathion
* NICOTINE SALTS	Insecticide	Black Leaf 40 and many trade names.	None Nicotine penetrates intact skin its salts do not	Salivation nausea vomiting tonic and clonic convulsions and death in respiratory paralysis	Symptoms within a few minutes. Death in a few minutes to a few hours.	Extremely toxic 1 mgm /kg orally	No specific antidote Wash off skin. Gastric lavage or emesis. Catharsis Control convulsions with pentobarbital
* PARATHION (Diethyl p-nitrophenyl thiophosphate)	Insecticide Organic phosphate group	E-605 Thiophos, Vapophos Alkron Compound 3422 DNIP DPP Genthion Niran Penphos	None Absorbed through intact skin.	Lacrimation salivation sweating nausea vomiting diarrhea respiratory distress miosis and later blurred vision abdominal cramps muscular tremors weakness tonic-clonic convulsions, coma and death in respiratory failure	Symptoms in 30 minutes death in several hours	Highly toxic 10 mgm /kg	Atropine sulfate 2 to 4 mgm IV as often as necessary Artificial respiration (Avoid mouth-to-mouth as secondary poisoning from victim may occur) See p 789 for use and doses of oxime compounds
PHOSDRIN (Alpha isomer of 2-carbomethoxy1 methylvinyl dimethyl phosphate)	Insecticide Organic phosphate group	O S 2046	None Absorbed through intact skin	See Parathion.	Not established	Highly toxic. Not determined Less toxic than parathion	See Parathion
* PHOSPHORUS	Rodenticide	Yellow phosphorus white phosphorus.	Skin burns Absorbed through intact skin	Nausea and vomiting garlic taste thirst pain in throat and stomach diarrhea headache weakness and collapse	Several hours to several days.	Highly toxic. 1 5 mgm./kg	No specific antidote. Gastric lavage General supportive measures
* PYRETHRUM (Dried flowers of *Chrysanthemum cinerariaefolium*) Active ingredients termed pyrethrines.	Insecticide Often mixed with other agents.	Insect powder Buhach	Mild sternutatory effect May give a contact dermatitis	Hyperexcitability incoordination tremors muscular paralysis with death due to respiratory failure	10 hours to 5 days	Slightly toxic. 1 5 gm /kg orally	No specific antidote Gastric lavage and cathartics A artificial respiration if indicated
RED SQUILL (The fleshy inner scales of the bulb of *Urginea maritima*)	Rodenticide	Squill	Irritating to skin	Violent emesis gastrointestinal colic and diarrhea	Several hours	Moderately toxic 3 gm orally	No specific antidote Gastric lavage and cathartics

ROTENONE (The poisonous principle of Derris root and roo)	Insecticide	Derris	Irritation of mucous membranes and conjunctiva		Numbness of mouth and throat, nausea and vomiting, at first stimulates then depresses respiration. Death from respiratory failure	Symptoms in few minutes, death may be delayed for days.	Slightly toxic 50 gm orally but much more toxic in finely divided form by inhalation	No specific antidote. Gastric lavage and cathartics.
SODIUM FLUOROACETATE ($CH_2FCOONa$)	Rodenticide	1080 ten-eighty	None		Nausea, vomiting, mental depression, epileptiform convulsions, irregularity of heart action, extreme depression, coma and death from respiratory failure	Symptoms in 30 minutes to 2 hours. Death in several hours	Extremely toxic, 50 to 100 mgm.	No specific antidote. Gastric lavage. Pentobarbital may be used to control convulsions and monoacetin (glycerol monoacetate) 0.1 to 0.5 ml/kg of the 60% solution diluted 1:5 with saline I.V. Depression of respiration must be avoided
*STRYCHNINE (Often used as strychnine sulfate)	Rodenticide	Rodex poison wheat	None		Tightness in chest, spasms alternate with depression and violent convulsions, death in respiratory paralysis	A few minutes to a few hours	Highly toxic 20 to 30 mgm orally	Any rapid acting barbiturate by the intravenous route. Gastric lavage after convulsions are controlled
*SYSTOX (Diethoxy thiophosphoric ester of 2-ethylmercaptoethanol)	Insecticide Organic phosphate group	Demeton E 1059	None	Readily absorbed through intact skin	See Parathion.	Symptoms develop in minutes to hours. Death may occur as early as 1 to 2 hours	Highly toxic 100 mgm estimated as fatal oral dose in the adult	See Parathion
*TETRAETHYLPYROPHOSPHATE	Insecticide Organic phosphate group	TEPP, Bladex, Fosfex, Hexamite, Nifos, TEP, Vapotone	None		See Parathion	Extremely short. Death may occur in 30 to 60 minutes after exposure	Extremely toxic 0.4 mgm/kg	See Parathion
*THALLIUM SULFATE (Thallous sulfate)	Insecticide and rodenticide	Many trade names containing the term [illegible]	None		Pains and paresthesias, ataxia, ptosis, loss of hair, coryza, fever, abdominal pain, nausea and vomiting. Severe poisoning is indicated by lethargy, jumbled speech, tremors, choreiform movements and convulsions with death due to respiratory failure	Variable. Acute and chronic forms of poisoning	Highly toxic 0.5 to 1 gm	No specific antidote. Gastric lavage, cathartics. BAL may be useful. See Arsenic
*TOXAPHENE (Chlorinated Camphene)	Insecticide Chlorinated hydrocarbon group	Genphens A, Compound 3956, Toxakil	None	May be absorbed through intact skin	See Chlordane	Symptoms in 1 hour and death in 4 to 24 hours	Moderately toxic. About 60 mgm/kg orally	See Chlordane

* Fatal poisoning attributed to this particular agent

Table XI.11. Essential Information on Some Important Economic Poisons (Insecticides and Rodenticides) (Continued)

NAME	TYPE	SYNONYMS	LOCAL ACTION	SYMPTOMS OF POISONING	FATAL PERIOD	FATAL DOSE	TREATMENT FOR POISONING
WARFARIN (3-acetonylbenzyl 4 hydroxycoumarin)	Rodenticide	WARF 42 Compound 42.	None	Back and abdominal pain, bleeding from gastrointestinal and urinary tract purpura signs secondary to blood loss.	Several days after a single massive dose or after repeated daily doses	Slightly toxic. Serious illness after ingestion of 1 7 mgm/kg each day for 6 consecutive days. Probably a single dose would not prove fatal.	Transfusions and vitamin K the latter 65 mgm repeated 3 times the first day and daily thereafter
* XYLENE (Xylol dimethylbenzene)	Pesticide diluent and solvent	None	Severe irritant to mucous membranes and sensitive skin.	Headache disturbed vision dizziness poor muscular coordination nausea. Collapse and coma in severe poisoning. Chronic exposure may result in anemia, headache malaise loss of appetite fatigue	Unknown in acute poisoning. Weeks to months in chronic poisoning	Moderately toxic. Not determined	No specific antidote. Gastric lavage. Wash contaminated skin. Saline laxatives. 2% butyn sulfate ointment when eyes are contaminated. Symptomatic and supportive therapy as indicated

* Fatal poisoning attributed to this particular agent

peripheral nerve damage may result from repeated prolonged exposure to the organic phosphate insecticides

Atropine is a nearly specific antidote for poisoning by organic phosphates and vigorous treatment with it is essential Two to 4 mgm of atropine sulfate intravenously should be given as necessary titrating the signs of atropinization against those of organic phosphate poisoning Large total doses of atropine sulfate may be required to control the

intravenously) may help to establish the diagnosis The nonpoisoned individual will show signs of atropinization whereas the poisoned individual may not react Oxygen administration and artificial respiration may be required If convulsions interfere with respiration they may be alleviated with trimethadione (Tridione) 1 gram intravenously every 15

(2 PAM) and diacetyl

juncts to atropine in the management of anticholinesterase intoxication They should diminish the necessity for or duration of artificial respiration and endotracheal intubation Provisional doses are as follows In severe intoxication 2 grams of 2 PAM (500 mgm. per minute) or DAM (200 mgm per minute) intravenously with possible repetition of the dose if weakness is not relieved or recurs in moderate intoxication 1 gram intravenously repeated if weakness is not relieved or recurs

A summary of the essential information on the toxicity of various insecticides and rodenticides appears in Table XI 11

Laboratory Aids in Pesticide Poisoning

The clinical laboratory can aid in the diagnosis and treatment of

led blood cell and plasma cholin

useful to prove poisoning This enzyme analysis may also be employed to diagnose cases of subclinical poisoning

2 *Warfarin Poisoning* A markedly reduced plasma prothrombin activity is to be expected in Warfarin poisoning

3 *DDT Poisoning* A fat biopsy may be subjected to chemical analysis for DDT storage This technique is useful with some other chlorinated hydrocarbons

4 *Arsenic Poisoning* The Reinsch screening test is rapid enough to be of value in establishing the diagnosis This test may be applied to the urine

5 *Dinitrophenol Poisoning* An increased basal metabolic rate in the absence of signs and symptoms of hyperthyroidism might be presumptive evidence of dinitrophenol poisoning A fairly simple chemical determination for blood and urine levels of dinitro ortho cresol is available

6 *Pyrethrum Poisoning* Patch tests using pyrethrum may be of help in diagnosing hypersensitivity to this agent

XII

Some Laboratory Diagnostic Methods

77

Methods and Procedures

I. General Procedures

Introduction

This section gives concise instructions for performing some of the laboratory tests used in the diagnosis of important tropical diseases Some examples have been chosen for their excellence in producing the desired results others have been selected for their applicability to small laboratories with limited equipment In fact, many of the tests may be performed in the field For the details of elaborate laboratory procedures the reader is referred to standard texts on the subject

1 Preserving and Packing Pathologic Tissues for Shipment

a Formalin Fixation Blocks of tissue of about 0 5 cm or less in thickness are dropped into 25 to 50 times their volume of 10 per cent formalin solution in distilled water (formaldehyde 37 per cent by weight is 100 per cent formalin) Fix for one or two days and transfer to 5 per cent formalin

b Zenker Fixation. Zenker's is one of the best fixatives for pathologic tissues in general

1 Fixing Solutions

Solution A

Potassium dichromate	25 gm
Mercuric chloride	50 gm
Sodium sulfate (sometimes omitted)	10 gm
Distilled water	1000 ml

Solution B

Glacial acetic acid

Before use mix by volume—

Solution A	95 parts
Solution B	5 parts

This mixture deteriorates upon standing

2. Procedure Blocks of tissue of 0 5 cm thick are left in fixative for 24 hours, then washed in running water for 24 hours If piped water is not available the tissues may be washed in a brook in cheesecloth sacks or beakers containing tissues may be decanted frequently and refilled with water After being washed tissues are transferred to 50 per cent alcohol for 3 hours, then to 70 per cent for preserving and shipment A

pencilled note inside container should accompany tissue, indicating its nature, fixing agent and that it is preserved in 70 per cent alcohol but has not been treated with iodized alcohol

c. Shipping. Fixed tissue blocks are wrapped in cheesecloth and either packed in cotton saturated with the preservative (usually 70 per cent ethyl alcohol) or placed directly in jars of the preservative which are completely filled with fluid and carefully stoppered

2 Preserving and Packing Protozoa, Helminths and Helminth Eggs from Feces

a. Protozoan Cysts and Worm Eggs in Feces. Dilute feces with tap water to a watery consistency, then pour simultaneously with an equal volume of hot (80° C) 10 per cent formalin into a separate vessel Let stand a few hours, decant, and replace with 5 per cent formalin Bottle, pack, and ship Formalinized protozoan cysts stain well with iodine Cysts of some protozoa and eggs remain well preserved for at least a year Frequently cysts of *E histolytica* and *I butschlii* do not preserve satisfactorily

Feces may be preserved in PVA fixative and shipped

b. Fecal Smears Coverglasses with fecal smears fixed in Schaudinn's fluid (see p 813) are packed for shipping in 70 per cent alcohol between lens paper in widemouth bottles completely filled with the alcohol Include data giving source of material, method of fixation and whether it has been treated with iodine

Smears may also be preserved in PVA fixative

c. Helminths. Dead helminths of all types obtained at autopsy or *roundworms from stools need only be washed in lukewarm physiologic* salt solution and dropped into hot (80° C) 5 per cent formalin for preservation

Live worms such as large tapeworms or ascarids may be allowed to die in cold water before fixation in hot 5 per cent formalin If allowed to stand too long after death, degenerative changes (such as blistering or fraying of cuticle) will occur Tapeworms may also be washed in physiologic salt solution, wrapped around a spool or a glass plate while still alive and immersed in 3 per cent formalin Small live nematodes and flukes will frequently become extremely distorted if dropped directly into fixatives, a preliminary fatiguing process consisting of prolonged shaking of the worms in physiologic salt solution is sometimes necessary When relaxed they are dropped into 70 or 80 per cent alcohol made up with 3 to 5 per cent glycerin and heated to 60° C The label should indicate the nature of the fixative so that the recipient of the shipment can mount the worms in glycerin merely by slow evaporation of the alcohol

Pack for shipment as indicated for pathologic tissues (see above)

3 Preserving and Packing Arthropods for Shipment

Insects and other arthropods of medical importance should be collected whenever possible for study and identification Full data for each

collection such as date locality elevation host habitat and collector should be included

a **Aquatic Larvae Especially Mosquito Larvae** (1) Kill in any manner to prevent distortion such as immersion in hot water for 10 to 20 seconds or in a mixture of borax formaldehyde and then transfer to 50 per cent and subsequently to 70 per cent alcohol

(2) Pack carefully by placing larvae in small vial or in short lengths of ordinary glass tubing Fill with alcohol and stopper with cotton at both ends in the latter case being careful to exclude *all* air bubbles A number of such tubes may be packed in cotton in a larger alcohol filled container which *should* contain an air bubble to allow for changes in pressure

b Adult Diptera Especially Mosquitoes (1) Collect at least 10 of each sex and kill with chloroform or cyanide collecting tube Reared specimens should be kept alive for 5 or 6 hours to allow them to harden

(2) Adults are delicate and must be packed as soon as possible after killing by placing in pill boxes or the like between layers of cellucotton lens paper cleansing or soft toilet tissue Pack to prevent movement *Do not use ordinary absorbent cotton*

(3) The above applies also to gnats sandflies and other mosquito like insects

c Other Arthropods 1 Large forms such as house flies may be preserved in 70 per cent alcohol Also use alcohol for all wingless forms such as hard ticks mites fleas spiders and maggots Soft ticks may be shipped alive in well stoppered vials

d Shipping Pack carefully in such a manner as to avoid breakage and forward for identification

4 *Making Thick and Thin Blood Films*

a Cleanse ear lobe or fingertip with gauze saturated with 70 per cent [illegible] rong spirits may be sub stit ite [illegible] dry

b I [illegible] Bard Parker detachable blade or disposable blood lancet deeply enough to cause free flow of blood Discard first drop

c Collect 3 or 4 small drops in small area near one end of clean glass slide Stir them together with corner of another clean glass slide Area covered by film should be the size of a dime thickness such that news print can barely be read through it

d Make thin smear on remaining slide surface

e Place in slide box and allow to dry thoroughly in horizontal position Thick drop may require 2 hours or more to dry (especially in the tropics) Protect from dust flies cockroaches

5 *Use of Anticoagulants*

If large numbers of smears are desired from the same patient or if clotting is to be prevented one of several anticoagulants may be used as follows

Thick films are automatically laked while staining in an aqueous dilution of stain

(3) *Thick and Thin Smears* These may be stained together on the same slide, *using caution not to fix the thick smear*, stain as outlined above

3 Wright's Stain for Blood

a. Stock Solution.

Stain (powdered)	0 3 gm
Glycerin (C P)	3 0 ml
Methyl alcohol absolute acetone free	97 0 ml

Grind powdered stain and glycerin together When well mixed add the methyl alcohol and stir well Place mixture in a tightly stoppered brown glass bottle for 2 to 3 weeks then filter and the stain is ready for use This stain improves considerably with age

b. Staining Procedure. (1) *Thin Smears* (*a*) Rule off area covered by the blood film with a wax pencil

(*b*) Cover dried film with stock stain for 1½ minutes (this fixes the blood film)

(*c*) Add an equal amount of freshly distilled or buffered water (*p*H 6 8) Stain for 3 minutes

(*d*) Wash by flooding with distilled or buffered water Stand on end to dry

(2) *Thick Smears* In staining thick smears it is first necessary to lake the red blood cells This is done by simply immersing thick film in H_2O until the hemoglobin stops running out and smear appears gray Allow to dry, then stain as for thin films

4 Field's Rapid Method for Staining Malarial Parasites in Thick Blood Films

In this method thick blood films are stained in such a manner that the stained parasites and leukocytes are contrasted against a homogeneous background After staining differentiation of color is more clearly shown in lower edge of the film toward which the hemoglobin has drained Reduced hemoglobin content of the blood increases the staining time necessary to as much as 10 seconds in cases of severe anemia

a. Preparation of the Blood Films. Blood films should be about the size of a dime and not too thick Films are ready to stain as soon as they are no longer obviously moist Fixation is not necessary *Freshly* prepared blood films stain better than when a day or two old

b. Preparation of the Stains

Solution A	
Methylene blue	0 8 gm
Azur B (American stains)	0 5 gm
Disodium phosphate (anhydrous)	5 0 gm
Potassium phosphate monobasic (anhydrous)	6 25 gm
Distilled water	500 mL
Solution B	
Eosin	1 0 gm
Disodium phosphate (anhydrous)	5 0 gm
Potassium phosphate monobasic (anhydrous)	6 25 gm
Distilled water	500 ml

The phosphate salts are first dissolved then the stain is added Solution of the granular Azur B is aided by grinding in a mortar with a small quantity of the phosphate solution Solutions of stain should be set aside for 24 hours when after filtration they are ready for use The same solutions may be used for many weeks without deterioration but the eosin solution should be renewed when it becomes greenish from a slight carryover of methylene blue

c Staining Procedure (1) Dip film for one second into solution A

(2) Remove from solution A and immediately rinse by waving *gently* in clean water for a few seconds until the stain ceases to flow from the film and the glass of the slide is free from stain

(3) Dip for 1 second into solution B

(4) Rinse by waving *gently* for 2 or 3 seconds in clean water

(5) Place vertically against a rack to drain and dry

The concentration of the stain is adjusted for staining times of 1 second with an immediate wash of 5 seconds but relative times may need slight adjustment to suit different batches of stain

5 Hematoxylin Staining of Thick Films for Microfilariae

Hematoxylin stains the sheaths of microfilariae better than do Giemsa's or Wright's stains

a Preparation of Delafield's Hematoxylin.

Hematoxylin crystals	4 0 gm
95% ethyl alcohol	25 0 ml.

Dissolve the crystals in the alcohol and mix the solution with 400 ml of a saturated aqueous solution of ammonium alum

Place in loosely capped container and keep in a light airy location for 2 weeks Then add mixture of—

Methyl alcohol (acetone free)	100 ml
Glycerin	100 ml

Bottle and expose to direct sunlight for at least a month Filter before use

b Staining P[illegible] film as previously on glass slide

(3) Allow to air dry

(4) Fix in equal parts of ether and 95 per cent alcohol for 10 minutes

(5) Allow to air dry

(6) Stain with Delafield's hematoxylin for 10 to 12 minutes

(7) Destain in water made slightly acid with HCl

(8) Wash in running water until blue color appears in film

(9) Air dry Mount in any *neutral* mounting medium

When microfilariae are observed in Giemsa's stained preparations they should be *destained in acid alcohol washed thoroughly and then* stained according to the above directions

6 Modified Gram's Stain for Spirochetes

This stain was used originally for the spirochete of Vincent's infection but can be used also for relapsing fever organisms

a. Procedure (1) Fix smear (as swab smears from Vincent's infection or laked thick blood smears) by passing once or twice through flame

(2) Flood with gentian violet (1 per cent aqueous solution) add 5 drops of sodium bicarbonate (5 per cent solution fresh or made previously with 1 20 000 merthiolate), allow to stand for 30 seconds

(3) Wash quickly in water

(4) Flood smear with iodine solution (iodine 1 gram potassium iodide 2 grams distilled water 200 ml) for 1 minute

(5) Rinse slide in water stand on end to air dry

(6) Examine with oil immersion lens Spirochetes and fusiform bacilli stain dark purple

7 India Ink Method for Spirochetes and Cryptocccus

a Staining Procedure (1) Mix a bacteriologic loop of fluid containing spirochetes or fungi with a small drop of India ink

(2) Smear and allow film to air dry

(3) Examination reveals the general shape of the organism as a clear figure in a dark background This is not a staining method in the true sense

8 Macchiavello Stain for Rickettsiae

a Fixing and Staining Procedures (1) Smear material to be stained on a clean glass slide

(2) Fix the smear by heat

(3) Flood with basic fuchsin 0 25 per cent for 5 minutes drain

(4) Flood with citric acid 0 5 per cent and wash immediately with tap water

(5) Counterstain with methylene blue medicinal 1 0 per cent for 20 to 40 seconds Rickettsiae appear bright red against a blue background This stain is not useful in demonstrating rickettsiae of scrub typhus

9 Examination of Fresh Blood

a Procedure (1) Collect a small drop of blood from ear lobe or fingertip on slide

(2) Superimpose cover glass immediately press gently to distribute blood evenly and thinly Examine with the microscope

(3) Trypanosomes microfilariae and spirochetes betray their presence by jostling the red cells Malaria is recognized by pigment granules within the erythrocytes which particularly in *Plasmodium vivax* may be carried about by cytoplasmic streaming of the parasite

10 Examination of Tissue Aspirates

a Procedure (1) Fluid aspirated from lymph nodes may also be examined in the fresh state for trypanosomes or microfilariae

(2) Aspirates from splenic punctures (kala azar) or from the indurated margin of ulcers (dermal leishmaniasis) should be smeared and stained as blood smears Examine for leishmanial bodies

11 Dark Field Illumination for Spirochetes and Leptospiras (from TM 8–227)

a General Observation of living spirochetes in transmitted light

is very difficult Organisms should be brought into view by a special dark field condenser which gives concentrated oblique illumination by a "funnel stop" inside the oil immersion objective which reduces the amount of direct light A special light source is needed as daylight is not sufficiently intense

b **Adjustment of Apparatus** (1) Remove the ordinary condenser and insert the dark field condenser with its 2 lateral adjustment screws forward

(2) Adjust the source of light until a bright ring or spot appears on the upper surface of the condenser the plane mirror is used

(3) With the low power objective locate the top of the condenser and the ring etched on the surface of the condenser

(4) Manipulate the lateral adjustment screws until the ring is brought into the center of the field

(5) Remove the lower half of the oil immersion objective, insert the funnel stop with its small end towards the lens and reassemble the objective.

c. **Procedure** (1) Secure clean slides 1 45 to 1 55 mm thick and clean cover glasses

(2) Rim the coverglass with a small amount of petroleum jelly

(3) Place a small drop of the fluid to be examined on the center of the slide apply the cover slip and press down to obtain a thin film avoiding bubbles

(4) Lower the substage slightly and place a drop of immersion oil free of bubbles on the upper surface of the condenser

(5) Put the slide preparation on the mechanical stage and center the specimen

(6) Raise the substage until the oil is spread by contact with the slide

(7) Place a drop of immersion oil free of bubbles on the cover slip.

(8) Lower the oil immersion objective focus on the microorganisms which should appear as bright objects against a black background Adjust the light for brilliant illumination reducing if necessary with the condenser diaphragm

12 Centrifugation Methods for Trypanosomes

a. **In Blood.** (1) Mix 9 ml of blood and 1 ml of 6 per cent sodium citrate

(2) Centrifuge at 1500 r p m for 10 minutes

(3) Remove small amount of thin creamy layer between red cells and supernatant with a capillary pipette and examine or

(4) Transfer leukocytic cream and supernatant to another tube and spin at 1800 to 2000 r p m for 15 minutes

Examine sediment directly under microscope or

Make smears lake fix and stain with Giemsa s

b **Cerebrospinal Fluid** (1) Spin 5 ml of spinal fluid at 1800 for 15 minutes

Examine sediment directly or

Make smears lake fix and stain

13 Centrifugation Methods for Nematode Larvae in Blood and Spinal Fluid

a. In Laked Blood. *Knott's Modified Survey Method* (1) Collect exactly 1 ml of venous blood

(2) Mix with 10 ml of 2 per cent formalin in a 15 ml centrifuge tube Blood lakes at once

(3) Centrifuge, or allow to sediment for 15 to 18 hours

(4) Decant supernatant fluid from sediment by quick tipping of tube so as to pour off surface bubbles

(5) Holding tube inverted, aspirate sediment with a capillary pipette

(6) Spread sediment into square area size of 22 mm coverglass air dry

(7) Fix in equal parts of ether and 95 per cent alcohol for 10 minutes, air dry

(8) Stain with Delafield's hematoxylin for 40 to 60 minutes

(9) Rinse quickly in 0 05 per cent HCl

(10) Wash in running water until blue color appears in film, air dry

(11) Add immersion oil with or without cover glass and search for parasites under low power, confirm under oil

b. In Citrated Blood. (1) Mix 5 ml of freshly drawn blood and 1 ml of 2 0 per cent sodium citrate made up in 0 85 per cent sodium chloride solution

(2) Centrifuge at 1000 r p m for 10 minutes

(3) Pass a fine pipette through the red cell sediment to remove material on bottom of tube

(4) Spread this sediment on a glass slide and examine for active microfilariae with low power of the microscope, also examine the buffy coat for microfilariae

c. In Cerebrospinal Fluid. (1) Five to 15 ml of fluid is centrifuged at 1000 r p m for 5 or 10 minutes

(2) Examine sediment under low power of the microscope for living *Trichinella* larvae

14 Examining for Superficial Fungi

a. Procedure. Hair should be removed from lesion by forceps skin should be scraped from periphery of lesions or obtained from roof of vesicles with curved manicure scissors, nails should be scraped where friable or discolored, and detritus beneath nail collected

These materials may be placed between 2 sterile glass slides, wrapped in paper and allowed to desiccate from 5 to 7 days before culturing or may be cultured directly after microscopic examination has revealed the presence of fungi

b. Microscopic Examination. (1) Clear collected material in 10 to 40 per cent potassium hydroxide by placing a small fragment of hair, skin or nail on slide in a drop of potassium hydroxide, add coverglass

(2) Heat gently over a low flame of Bunsen burner or alcohol lamp to hasten clearing process

(3) Examine under low or high dry power of a compound microscope oil immersion is rarely needed

From material found to contain fungi other specimens should be cultured on Sabouraud's glucose agar slants by placing two or three fragments on each slant (see p 824 for further details)

15 Examining for Systemic Fungi

Sputum pus and spinal fluid should be examined in the fresh state without the addition of a clearing agent to avoid artifact formation. A loop full of sputum or pus should be placed on a slide and gently pressed to a thin film under a coverglass Spinal fluid itself may be examined directly or the centrifuged sediment may be examined These materials should be mixed with a drop of India ink to demonstrate capsule formation if *Cryptococcus neoformans* is suspected (see p 800) Examine all preparations with reduced light from the microscopic condenser

All material should be cultured on Sabouraud's glucose agar at room temperature and beef infusion blood agar at 37° C Hold all cultures for at least three weeks If *Actinomyces bovis* is suspected beef infusion glucose agar shake cultures should be inoculated to obtain a culture of this microaerophylic fungus (see p 824 concerning cultures)

16 Lactophenol Cotton Blue for Staining Fungi

Lactophenol cotton blue is prepared as follows

Phenol crystals	20 gm
Lactic acid	20 ml
Glycerin	40 ml
Water	20 ml

Heat gently under a hot water tap to dissolve Add 0 05 gram cotton blue (C_4 Poirrer)

Use as directed (see p 800) for staining fungi

III. Method for Obtaining and Examining Duodenal Drainage Fluid for Strongyloidiasis and Other Parasitic Infections

a Procedure (1) A standard Rehfuss tube with olive tip is used. Tube is passed (*through the mouth*) with the patient in a sitting position It is passed until it reaches the stomach This is indicated when the marking of *1 ring* on the tube is at the level of the patient's lips Stomach contents are then aspirated (with a 30 ml syringe) Patient is then placed in a lying position on his right side This position is very important The patient is then instructed to swallow the tube farther down at a slow rate approximately 1 to 2 inches every 5 to 10 minutes—until the marking showing *3 rings* on the tube is at his lips Usually during this period clear or cloudy gastric juice will flow and this may be discarded After a period which varies with each patient a clear light yellow material will flow. The patient then should be stimulated ... or olive oil may be used Approximately 30 ml of 33 ... magnesium sulfate is introduced into the duoden...

and allowed to flow back into a test tube immediately If the procedure has been properly carried out dark bile will follow the returning magnesium sulfate This procedure may be repeated as often as is necessary

(2) If difficulty is encountered in getting the tube into the duodenum a few simple aids may be tried

(*a*) Use a pillow to elevate the patient s hips

(*b*) Turn the patient on his left side for 5 to 10 minutes then return him to original position

(3) Two simple ways of determining the position of the tube are as follows

(*a*) The patient is given a small amount of water by mouth and a syringe is attached to the free end of the tube If water can be aspirated the tube is in the stomach and must be returned to stomach depth (that is pulled out until the marking of *1 ring* is at the level of the patients lips The progressive swallowing process outlined above should then be repeated

(*b*) Attach a syringe to the free end of the tube and attempt to aspirate If a vacuum is formed and you are unable to aspirate the fluid it is safe to assume that the tube is in the duodenum or in the pylorus approaching the duodenum

b Identification of Intestinal Parasites (1) Intestinal parasites may be found in A B or C bile but are detected most frequently in C bile (darkest bile) In most instances the parasites are located in the mucoid content of the bile They should be sought in the *mucus suspended in the bile* and in the sedimentated mucus Some of the mucus usually settles to the bottom of the container after standing for a few minutes Because of the viscosity of bile centrifugation is of no significant aid in this procedure The dark bile stained drainage fluid may be placed in a conical sedimentation jar or in a pilsener glass Transillumination of the fluid by placing a microscope lamp behind it aids in the visualization of the suspended mucus fragments which should be examined microscopically The floating and sedimentated mucus may be removed for examination by use of a large caliber pipette with a rubber bulb The material is placed on a glass fecal slide and examined under low power Several slides should be examined before calling the drainage fluid negative for strongyloidiasis

(2) The three parasites most frequently found are *Strongyloides stercoralis* *Giardia lamblia* and hookworm In the case of *Strongyloides stercoralis* if [illegible] nt find ing will be th[illegible] he egg These are usu[illegible] ion the slide may be set aside at room temperature for 10 to 15 minutes during which time the larvae will hatch A drop of iodine may be added before examination so that the buccal cavity may be more readily visible If the material to be examined has been standing for 15 to 30 minutes the larvae will have already hatched but will still be found in the mucoid content of the bile In the case of *Giardia lamblia* the trophozoites will be

present In hookworm infection eggs in various stages of clea
seen

IV Methods of Examining Feces for Protozoa and Helm

1 Direct Smears—Saline and Iodine Stained Smears

a Preparation of Iodine Stain (after D Antoni)

(1) A suitable iodine stain may be prepared by mixing the fo

Potassium iodide	1.0 gm
Iodine crystals or powder	0.5 gm
Distilled water	100 ml

Some prefer to add 1 ml of glacial acetic acid per 100 ml of water

b. Procedure

(1) Place a drop of physiologic saline in the center of one half of slide (some prefer a 1½ x 3 inch slide) and a drop of iodine stain the other half

(2) Examine the stool for blood or mucus and carefully select m terial from those areas as well as from several others and spread *evenly* throughout the saline over one coverglass width of the slide Newsprint should be just legible through the smear after applying cover glass

(3) In the same manner additional fecal material is spread in the drop of iodine

(4) A coverglass is then applied to each of the smears and the prep rations are examined Thus 2 coverslip preparation should always be employed when stools are examined microscopically

(5) The entire area of the 2 smears on the fecal slide should be exam ined systematically with low power The high dry magnification is em ployed to study objects suggestive of parasites It is profitable even for experienced personnel to examine a part of each smear with the higher magnification This will reduce the chances of overlooking small or ganisms *Furthermore a careful methodical and diligent search is re quired not merely a glance* Frequently amebae are not numerous in the stool

(6) The unstained (saline) side of a fecal smear is of greater value for detecting the presence of cysts or of trophozoites than the iodine stained portion of the fecal smear There is greater contrast between the refractile amebae and their background in the saline smear than in the iodine smear In the latter the amebae and the background both acquire a somewhat similar hue Amebic trophozoites if fresh and motile are recognized principally in the saline portion of the smear Cysts usually can not be specifically identified in the unstained side unless as occasionally appens chromatoid bars are present

(7) Iodine staining will kill trophozoites of protozoa and is not rec mmended for identifying worm eggs However it is invaluable ding amebic and flagellate cysts as nuclei and gl erwise almost invisible are thereby stained

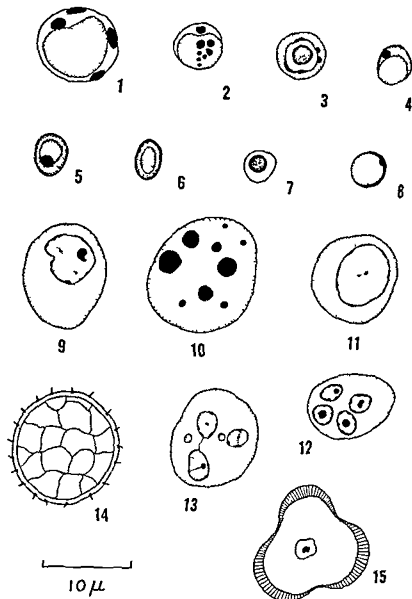


Figure XII 1 Various structures which may be seen in stool preparations 1 2 4 *Blastocystis hominis* 3 5 6 7 8 various yeasts 9 11 squamous cells from rectal mucosa 10 deteriorated macrophage without nucleus 12 13 polymorphonuclear leukocytes 14 15 pollen grains" (Markell & Voge Diagnostic Techniques in Medical Parasitology)

c Artifacts It is always necessary to be alert to the possibility of confusing some yeast plant or tissue cell with an ameba A few of the more commonly encountered artifacts of the stool appear in Figures XII 1 and XII 2

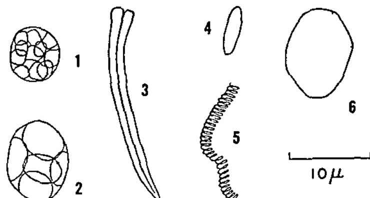


Figure XII.2 Plant structures seen in the stool 1 2 aggregates of starch granules 3 plant hair 4 6 amorphous vegetable materials superficially resembling eggs or protozoan cysts 5 vegetable spiral (Markell & Voge Diagnostic Techniques in Medical Parasitology)

2 *MIF (Merthiolate-Iodine Formalin) Stain and Fixative for Intestinal Protozoa and Helminth Eggs (after Sapero and Lawless)*

Both cysts and trophozoites are stained in a solution which also acts *as an effective preservative*

a For Staining the Cysts and Trophozoites of Fecal Specimens Brought to the Laboratory (1) *Preparation* (*a*) Place in a Kah [illegible] fecal examination [illegible] ution (USP) 0 77 [illegible] and 10 ml freshly prepared Lugols solution 5 per cent (Merck Index) (Note If Lugols solution is over 1 week old increase 0 10 ml to 0 125 ml if over 2 weeks old increase to 0 15 ml Reduce merthiolate in same amount that Lugols solution is increased Do not use Lugols over 3 weeks old)

(*b*) Place Kahn tube with 1 ml of stain and a second Kahn tube containing distilled water in a rack Put medicine dropper in each tube

(2) *Procedure* (*a*) Place a small drop of distilled water at one end of a glass slide add equal size drop of stain solution To this drop add feces and make a wet smear as described for the direct saline smear

b For Collection and Preservation of Specimens in Survey Studies Hospital *Wards Homes and for Mailing to a Laboratory* (1) *Preparation* Freshly prepare a 5 per cent Lugols solution and a stable stock "MF" solution containing 250 ml distilled water 200 ml tincture merthiolate (No 99 Lilly 1 1000) 25 ml solution formaldehyde USP 5 ml glycerin to make 480 ml stock "MF" solution (store in brown bottle)

(2) *Procedure* (*a*) Measure 2 35 ml "MF" stock solution into a standard Kahn tube and stopper with cork

(*b*) Measure 0 15 ml Lugols solution (5 per cent) into a second

Kahn tube and stopper with a rubber cork The two tubes represent a collection unit

(*c*) Immediately upon collecting a stool pour the "MF" solution into the Kahn tube containing the Lugols solution *The two solutions must not be combined until just prior to the addition of the fecal specimen* Using an applicator stick add and thoroughly stir into the solution a portion of feces about twice the volume of a medium sized pea (about 0 25 gm) Do not overload with feces Stopper the tube and record pertinent data on label

(*d*) To examine With a medicine dropper draw off a drop of fluid and feces from surface layer of sedimented feces Observations indicate that most species of protozoa and helminth eggs tend to concentrate on the upper layer of the sedimented feces Place drop on a glass slide Mix the fecal particles in the drop thoroughly by means of an applicator stick crushing any large particles Cover and examine

c Preservation of Larger Samples of Feces for Teaching Purposes or for Helminth Eggs or Protozoal Concentration Procedures (1) Use screw type cap vials to prevent evaporation Feces "MF" stock solution and Lugols solution may be placed in vials in proportions as follows

	AMOUNT OF FECES	M F SOLUTION	LUGOL S SOLUTION
(small)	0 25 gm	2 35 ml	0 15 ml
(med um)	0 50 gm	4 70 ml	0 30 ml
(large)	1 00 gm	9 40 ml	0 60 ml

Lugols solution should not be over 3 weeks old and should never be added to "MF" stock solution until just before the feces is to be added Prior addition of iodine to "MF" stock solution will cause a dense precipitate to form upon standing

(2) *Procedure* (*a*) Remove a drop of intermixed fluid and feces from sedimented surface layer make coverslip preparation and examine Preparation may be ringed with sealing materials

(*b*) For flotation concentration of helminth eggs replace supernatant fluid in vial specimen with saturated brine solution and proceed as usual for recovery of eggs

d Important Principles in Usage of Technique Staining Characteristics (1) By placing feces in solution *within 5 minutes of passage* the major disadvantage of loss of organisms and morphology deterioration which occur in most stools which are allowed to stand may be prevented As an example *D fragilis* and flagellates frequently largely lost in iron hematoxylin stained mounts are recovered in undiminished density by immediate fixation in MIF solutions

(2) *Staining* (*a*) Staining reaction comprises an initial iodine phase as seen in ordinary iodine preparations with the exception that both cysts and trophozoites are stained and a subsequent eosin stage which gradually replaces the iodine A reversal to the iodine phase if desired may be accomplished by addition of fresh Lugols to specimen i e by adding a drop of fresh MIF solution In trophozoites from patients

with amebic dysentery, red blood cells are even more readily defined than in fresh saline preparations

(*b*) Trophozoite forms stain immediately, cysts take stain more slowly An increase in the strength of Lugol's, or use of a more freshly prepared Lugols solution, will speed the staining time of cysts

3 Concentration of Cysts and Eggs by Zinc Sulfate Centrifugation Flotation (after Faust, et al.)

This method is good for cysts of amebae and flagellates and for some eggs *Strongyloides* larvae likewise are usually brought to the surface However, cysts are more distorted than with the formalin–ether sedimentation technique

a. Procedure. (1) Thoroughly comminute a stool sample the size of a small pecan in 2 or 3 ml lukewarm tap water in a Wassermann tube

horoughly with applica

d stir as before, centrifuge

(4) Repeat (3), may omit if supernatant is clear

(5) Decant water, replace with ¼ tube of zinc sulfate solution (Granular $ZnSO_4 7H_2O$ U S P, dissolve 331 gm in 1 liter of water to give the solution a specific gravity of 1 180—it should be checked with a hydrometer) stir thoroughly, fill to ¼ inch of brim of tube and spin at 2500 r p m for 45 to 60 seconds Allow centrifuge to stop smoothly Wait 1–2 minutes

(6) transfer the surface film onto a

(7)

If the examination is intended for protozoan cysts, loop surface film into a drop of iodine solution

4 Concentration of Cysts, Eggs and Larvae by Centrifugation Sedimentation

a. Formalin Ether Sedimentation—406th MGL (Med. Gen. Lab) Method (after Ritchie) This is the method of choice for general use It concentrates helminth larvae, eggs and protozoan cysts

(1) *Preparation* Keep ether refrigerated except when in use Prepare a 10 per cent solution of formalin

(2) *Procedure with Fresh Specimens* (*a*) Partial comminution of entire stool, with an appropriate amount of water or saline can be accomplished in the stool container Add enough fluid to make it possible to recover 10 ml of strained emulsion, which when centrifuged, will yield ½ to 1 ml of fecal sediment

(*b*) Strain through two layers of gauze and collect in a 15 ml pointed centrifuge tube A cone-shaped paper cup with the point cut off can be substituted for the glass funnel (Straining may be omitted to simplify the procedure if desired)

(*c*) Wash the emulsion with water or saline by centrifugation (1 minute at 2000 to 2500 r p m) decant the supernate

(*d*) Resuspend sediment in fresh water or saline centrifuge and decant as before

(*e*) Mix the remaining fecal sediment thoroughly with 10 ml of 10 *per cent formalin Allow 5 to 10 minutes* for fixation

(*f*) Add 3 ml of refrigerated ether to the formalinized specimen stopper and shake vigorously Then centrifuge specimen at 1500 r p m for about two minutes Four layers should be apparent ether at top plug of debris formalin solution and sediment Free the plug of debris from the centrifuge tube with an applicator and decant until only sediment at the bottom of the tube remains

(*g*) Thoroughly mix the sediment remaining in the tube with the fluid that drains back from the tube wall mix with applicator stick and pour onto a glass slide An applicator may be used to drag the few drops to the lip of the tube and is especially useful in controlling the amount of sediment that escapes *onto the slide An excess should* be avoided A small drop of iodine solution is placed near the drop of sediment and mixed with it by using the edge of the coverslip Finally the edge of *the coverslip is pushed into the drop allowing the fluid to run under the coverslip and at the same time pushing the coarse debris aside* This step is critical in obtaining a suitable microscopic preparation Examine under the compound microscope

b Formalin Ether with Preserved Specimens (after Brooke)

(1) Thoroughly stir formalinized specimen

(2) Depending on size and density of specimen strain a sufficient quantity through gauze into a 15 ml pointed centrifuge tube to give the desired amount of sediment indicated below (Straining may be omitted)

(3) Add tap water mix thoroughly and centrifuge at 2000 to 2500 r p m for 1 minute Resulting sediment should be about 1 ml

(4) Decant supernatant and wash again with tap water if desired

(5) Add about 10 ml of 10 per cent formalin to the sediment and mix thoroughly

(6) Add 3 ml of refrigerated ether stopper tube and shake vigorously *Remove stopper with care*

(7) Centrifuge at 1500 r p m for about 1 minute Four layers should result

(8) Free plug of debris from the sides of tube by ringing with an *applicator stick and carefully decant the top 3 layers*

(9) Mix remaining sediment with small amount of fluid that drains back from sides of tube and prepare iodine and unstained mounts in the usual manner for microscopic examination

c *Acid—Sodium Sulfate—Triton NE—*Ether Concentration*—AMS (Army Med Sch) Method** (after Hunter *et al*) This method is highly recommended for the detection of helminth larvae and eggs It is the method of choice for the detection of schistosome eggs

(1) *Preparation* (*a*) Prepare by adding approximately equal amounts of hydrochloric acid of a specific gravity of 1 089 (45 ml of

* Triton NE (Triton = X 30) is a wetting agent which may be secured from Rohm & Haas Co Philadelphia Penna at a nominal cost

concentrated HCl (37 per cent) and 55 ml of water) and sodium sulfate solution of a specific gravity of 1 080 (9 6 gm of anhydrous sodium sulfate to 100 ml of water) the final mixture having a specific gravity of 1 080

(*b*) In each solution adjust to the proper specific gravity if needed before preparing the final mixture which keeps four weeks or more

(*c*) To insure the best possible results it is advisable to dehydrate the sodium sulfate before using Dry in desiccator or a hot air oven (2 hours at 130° C) and cool in a desiccator

(2) *Procedure* (*a*) Partial comminution of the entire stool with an appropriate amount of water can be accomplished in the stool container Add enough water so that it will be possible to recover 10 ml of strained emulsion which when centrifuged will yield about ½ to

SO_4

cup

with the point cut off can be substituted for a glass funnel

(*c*) Wash by brief centrifugation (1 minute at 2000 to 2500 r p m) with HCl—Na SO_4 decanting the supernatant each time and mixing the sediment with fresh HCl—Na SO_4 repeat twice or until the supernate is clear

(*d*) After decanting add 5 ml of HCl—Na SO_4 plus 3 drops of Triton NE plus 3 ml of refrigerated ether Shake for 30 seconds and centrifuge for 1 minute at 1500 r p m Four layers should result ether at top plug of debris acid sodium sulfate solution and sediment

(*e*) Break ring at the interface with an applicator stick and decant

(*f*) Add tap water to the 0 4 mark mix sediment and pour as much as can be read onto a slide cover with a 24 by 40 mm coverglass An applicator may be used to draw the few drops of sediment to the lip of the tube and is especially useful in controlling the amount of sediment that escapes onto the slide

(*g*) Examine under the low power of compound microscope There should be a minimum of debris and the eggs should stand out clearly Some mature eggs will exhibit visible miracidia

5 *Quantitation of Worm Infections by Egg Counts*

Either Stolls dilution method or Beavers direct smear may be used for the estimation of worm burden They are mostly used for the evaluation of hookworm *Ascaris* and *Trichuris* infections but may be applied to any worm infection in which eggs or larvae are more or less continuously added to the bowel stream The main advantages in the smear method are that it is rapid and that it requires no correction for stool consistency *The chief disadvantage in the smear is that a calibrated specially* adapted photoelectric light meter is required However since smears made by experienced technicians are fairly uniform and nearly always contain between 1 and 2 mgm of feces worm infections can be determined roughly as heavy moderate and light without the use of a light meter Counts should not be made by either method on stools that are not made up of more or less normal fecal elements

a. Stoll Dilution Method. (1) *Material* (*a*) N/10 (0 4 per cent) sodium hydroxide solution

(*b*) Long necked Erlenmeyer flask marked to indicate 56 ml and 60 ml levels

(*c*) Glass beads, slides and 22 x 30 mm coverglasses

(*d*) Pipette calibrated to deliver 0 075 ml

(2) *Procedure* (*a*) Fill flask to 56 ml mark with sodium hydroxide solution

(*b*) Add feces to bring contents up to 60 ml mark

(*c*) Add glass beads or BB shot to nearly fill flask and stopper it

(*d*) Allow to stand 12 to 24 hours with occasional shaking

(*e*) Shake to thoroughly mix and withdraw exactly 0 075 ml

(*f*) Transfer to slide, cover and count eggs in entire preparation

(*g*) Eggs per preparation $\times$ 200 $\left(\text{i e}, \frac{4}{60} \times \frac{75}{1000} = 200\right)$ gives eggs per ml uncorrected

(*h*) Correct the count for stool consistency by multiplying uncorrected counts as follows $\times$ 1, for hard formed, $\times$ 1 5 for mushy formed (can be cut with applicator but holds shape against stroke against container), $\times$ 2 for mushy (can be compressed by stroke against container, $\times$ 3, for mushy diarrheic (takes shape of container but will not pour), $\times$ 4 diarrheic (can be poured)

b Beaver Direct Smear Method The ideal fecal smear for most purposes contains about 1 mgm of feces in 1 drop of water or physiologic saline solution Some workers prefer 2 mgm smears

(1) *Materials* (*a*) Any type of photoelectric light meter having a galvanometer dial and cell window on the same face and calibrated

(*b*) An adapter (handmade from wood or similar material having a thickness of about 18 mm) to reduce the cell window to a circular opening 16 mm in diameter

(*c*) Goose neck or other type of vertically adjustable lamp

(2) *Calibration Procedure* (*a*) Prepare 2N Na_2SO_4 and N/1 $BaCl_2$ solutions and mix each with ½ part pure glycerin

(*b*) Combine 1 part $BaCl_2$ mixture with 6 parts Na_2SO_4 mixture to give a white suspension of $BaSO_4$

(*c*) Place light meter apparatus directly under the lamp and adjust light to give an arbitrary whole number on the dial with a clean slide over the window

(*d*) Deliver 1 drop (0 05 ml) of the $BaSO_4$ suspension onto the slide above the window and spread just to cover the window

(*e*) The amount of reduction in the dial reading produced by the spread suspension (as compared with the clean slide) is that which will be produced by 1 mgm of formed feces in one drop (0 05 ml) of water or normal saline solution

(*f*) Calibration of instrument for making 2 mgm fecal smears is as above except 3 parts glycerinated Na_2SO_4 mixture to 1 part of the BaCl mixture are used to give a $BaSO_4$ suspension twice as heavy

(3) *Egg count Procedure* (*a*) Adjust light over meter to give

arbitrary predetermined "zero point" with clean slide in place over window

(*b*) Place 1 drop of water or physiologic saline solution on slide and spread to just cover the window

(*c*) Add feces from applicator by stirring until dial is shifted to 1 mgm point (or 2 mgm as desired) determined by previous calibration

(*d*) Cover with 22 x 22 mm coverglass and count eggs in entire preparation

(*e*) Counts can be recorded as eggs/mgm or eggs/gram (essentially the same as eggs/ml corrected to the formed stool basis) Infections giving counts of less than 5 hookworm or whipworm eggs or less than 20 *Ascaris* eggs per mgm feces generally are regarded as light, counts above 25 for hookworm or whipworm and 50 for *Ascaris* indicate heavy infections Interpretations must vary somewhat with circumstances such as age and condition of the patient, average bulk of the stool and duration of the infection

6 *Heidenhain's Iron Hematoxylin Staining of Fecal Smears* (modified from Brooke)

This is the best method of staining protozoa in fresh feces Properly prepared slides last many years Both long and short methods are described The standard long method gives excellent results if the procedure is carefully followed, especially with regard to destaining the organisms If the fixative, mordant and stain are heated, considerable time can be saved A special procedure is outlined for use in staining PVA fixed specimens (p 814)

a. Staining Solutions.

Schaudinn's Fluid

Saturated $HgCl_2$ solution in distilled water	64 ml
Absolute (or 95%) alcohol	*32 ml*
Acetic acid, glacial	4 ml

Iodine Alcohol

Prepare a stock solution by adding sufficient iodine crystals to 70% alcohol to produce a dark concentrated solution For use dilute some of stock solution with 70% alcohol until a port wine color is secured Exact concentration is unimportant

Mordanting Solution (Iron Alum)

Ferric ammonium sulfate	4 gm
Distilled water	100 ml.

Hematoxylin Stain—Stock Solution*

Hematoxylin powder	10 gm
Ethyl alcohol (95%)	100 ml.

* Dissolve powder in alcohol Keep several weeks to ripen before use Make staining solution by mixing 5 ml of stock solution with 100 ml of distilled water

b. Procedure. (1) Make a thin fecal smear with a toothpick or applicator on a clean slide or coverglass Dilute feces with physiologic saline if necessary Immediately immerse slide in Schaudinn's fixative, the *smear must not be permitted to dry from this point until it is mounted* However, if the staining schedule must be interrupted before or after

mordanting the slides may be stored in 70 per cent alcohol for long periods When interrupted between mordant and stain store slides in 70 per cent alcohol but repeat mordanting before completing staining

(2) Before a fecal smear dries gently immerse in Schaudinn s fluid and proceed as follows

	Rapid Method	*Long Method*
Schaudinn s	5 min at 50°C	60 min at room temperature
50% alcohol	3 min at room temperature	
70% plus iodine (wine color)	5 min at room temperature	
50%	3 min at room temperature	
Tap water	3 min at room temperature	
4% mordant (iron alum)	10–20 min at 50°C	12–24 hours unheated
2 changes in distilled or tap water	3 min (total)	
0 5% hematoxylin	5–10 min at 50°C	12–24 hours unheated
1–2% mordant (iron alum) to destain	Usually 1–3 min	

(Check carefully under microscope as this is the critical step every 30 seconds rinse in water to slow down destaining process and observe under the low or high power of the microscope The time varies with each smear even in same staining jar)

	Both Methods
Rinse in gently running tap water	5–30 min for permanent stain
70% alcohol containing a few drops of lithium carbonate	3 min unheated
95% alcohol	3–5 min unheated
Carbol xylene	3–5 min unheated
Xylene	3 min unheated

Mount with coverslip using Permount Clarite balsam or other neutral mounting media Examine when dry

c Interpretation of Stain (1) Well stained protozoa are grayish or bluish with black nuclei In the ameba chromatoid bars red blood cells and bacteria stain black Background appears blue gray

Trophozoites and cysts of protozoa are not usually distorted except in the cases of *Chilomastix and Trichomonas* The latter especially tend to

e been poorly fixed Fixing
2 will largely overcome this

except for *E coli* which requires fixation for 30 minutes at 56° C Fresh fixative even though cold yields sharper stained specimens but requires more time

7 *Polyvinyl Alcohol Fixative Method for Trophozoites of Intestinal Protozoa* (after Brooke and Goldman)

This method is specifically designed to preserve trophozoites of amebae for long periods of time in a condition suitable for subsequent identification It is fairly satisfactory for the detection of protozoan cysts

a Preparation *PVA Fixative* (1) Add 5 grams of polyvinyl alcohol* to a mixture at room temperature of 1 5 ml glycerol 5 ml

* PVA powder and solutions may be purchased in small quantities from Delkote Inc P O Box 1335 Wilmington Delaware

glacial acetic acid, and 93 5 ml of Schaudinn s solution (2 parts of saturated aqueous mercuric chloride to 1 part of 95 per cent ethyl al cohol) Heat gently while stirring to about 75° C or until the solution clears Solution keeps for several months at least

2 *Saturated Aqueous Picric Acid Solution* Add 2 grams picric acid crystals to 100 ml of water, shake Allow to stand for several days with intermittent shaking add more crystals if all dissolve Solution should be saturated in 3 to 4 days

b Procedure. (1) *Fixation in Vial* (*a*) Thoroughly mix 1 part of specimen in a vial containing 3 parts or more of PVA fixative

(*b*) Films for staining may be prepared immediately or months later by spreading a drop or two of the mixture on a microscope slide and allowing the smear to dry thoroughly (preferably overnight at 37° C) Films should be of moderate thickness

(2) *Fixation on Microscope Slides* (*a*) Mix thoroughly 1 drop of specimen with about 3 drops of PVA fixative on a microscope slide

(*b*) Spread the mixture over approximately one third of the surface of the slide and allow to dry thoroughly

(3) *Staining PVA Films* (after Brooke)

The Heidenhain s staining technique should be modified as follows

Place dry PVA film in 70% alcohol plus iodine	20 min
50% alcohol	10 min
Tap water	5 min
4% mordant (iron alum)	6–12 hrs
Tap water—2 changes	3 min (total)
0 5% hematoxylin	8–12 hrs or overnight
Tap water—2 changes	3 min (total)
Destain in saturated picric acid	15–20 min

(This step is critical The slide should be removed at interval washed in water and examined under low and high powers of the microscope (not oil) The time required varies with the individual smear)

Immerse in running tap water to stop destaining process	30 min
70% alcohol plus a few drops of lithium carbonate	10 min
95% alcohol	10 min
Carbol xylene	10 min

Mount with coverslip using Permount Clarite balsam or other neutral mounting media Examine when dry

(4) Interpretation of stain essentially as described elsewhere for Heidenhain s (p 814)

8 Diagnosis of Pinworm Infection

a. Procedure The most satisfactory means of diagnosing pin worm infection is by the recovery of eggs or female worms from the perianal region as only 5 to 10 per cent of infected persons pass eggs in their stools

(1) *Scotch Tape Method* (after Graham) (*a*) Prepare a swab with a 4 inch strip of Scotch tape ¾ to 1 inch in width and a standard 1 x 3 inch microscope slide One fourth inch of one end of the tape is folded upon itself to provide a nonadhesive area for handling The remainder is applied to the slide with the gummed side down extending

(2) Drop worms into glycerin alcohol fixative heated to 60° C in a small evaporating dish

(3) Set evaporating dish in a warm place to permit slow evaporation of the alcohol

(4) When alcohol appears to have entirely evaporated mount nematodes on slides in glycerin jelly

The intestinal structures will ordinarily stand out clearly Staining nematode worms is ordinarily not too successful and is not necessary

V. Methods of Examining Urine

1. *Examining Urine for Schistosome Eggs*

a. Procedure. (1) Collect urine sample for examination of eggs towards the end of micturition in sedimentation glass

(2) Allow to settle, pipette off bottom sediment to slide

(3) Examine microscopically for eggs of *S haematobium*

[illegible]

chyluria

2 *Examining Urine for Spirochetes*

Spirochetes of relapsing fever, *Leptospira icterohaemorrhagiae* or *L canicola* sometimes may be found in urine

a. Procedure. *(1) Collect 30 to 50 ml of urine in a sterile vessel*

(2) Centrifuge at 2000 r p m for 30 minutes

(3) Examine sediment under a dark field for spirochetes

Refrigerate (but do not freeze) urine sample if urine must be transported great distances

VI. Methods of Examining Sputum

1 *Examining Sputum for Helminth Eggs and Larvae*

a Mix sputum and 3 per cent sodium hydroxide solution in equal amounts

b Centrifuge at high speed

c Decant supernatant

d Examine sediment for eggs and larvae

Instead of sodium hydroxide, *Chlorox (full strength) may* be added in quantity sufficient to liquefy sputum

2 *Ziehl Neelsen Cold Stain for Acid Fast Bacilli* (after Aubert)

This stain is used to differentiate acid fast and non acid fast organisms and depends upon a primary stain, decolorizer and counterstain

a. Materials

(1) *Carbol Fuchsin Cold Stain*

Solution A

Basic fuchsin (90% dye content)	0 3 gm
Ethyl alcohol (95%)	10 0 ml

Solution B

Phenol	5 0 gm
Distilled water	95 0 ml

Mix solutions A and B

(2) *Loeffler's Alkaline Methylene Blue*

Solution A

Methylene blue (90% dye content)	0 3 gm
Ethyl alcohol (95%)	30 0 ml

Solution B

Dilute KOH (0 01% by weight)	100 0 ml

Mix solutions A and B filter

b Procedure. (1) Stain dried smears 10 minutes with carbol fuchsin

(2) Rinse in tap water

(3) Decolorize in 95 per cent ethyl alcohol containing 3 per cent by volume of concentrated HCl, until only a suggestion of pink remains

(4) Wash in tap water

(5) Counterstain with Loefflers alkaline methylene blue for about 1 minute

(6) Wash in tap water

(7) Dry and examine Acid fast organisms stain red, others blue

VII. Culture Methods

1 Membrane Filter Technique for Detection of Pathogenic Bacteria or Fungi (after Ellner)

a. Materials.

Filter holder
Membrane filters
Absorbent pads
(Obtainable from Millipore Filter Corporation Watertown Mass)
Filter flask
Vacuum source
Appropriate liquid media double strength
Petri dishes

b Procedure.

(1) The specimen (urine spinal fluid, laked blood etc) is filtered by means of suction through a previously sterilized membrane filter

(2) After the specimen has passed through the membrane filter, the filter is aseptically removed from the holder and placed in a sterile petri dish on top of an absorbent pad which has been saturated with double strength liquid media

(3) The plates are incubated in the usual manner Colonies appear on the surface of the membrane filter analogous to their appearance on solid media The advantages of this method are that a higher number of positive recoveries are obtained, growth appears faster, and frequently in pure culture

2 Boeck Drbohlav's Locke-Egg Serum Medium

This medium may be employed for the cultivation of *Entamoeba histolytica, Dientamoeba fragilis, Trichomonas hominis* and to a limited extent, some other species of intestinal amebae and flagellates Transfers are made every 48 hours About 0 5 ml of the fluid medium at the bottom of the tube is used for each transplant

a. Materials Required.

(1) *Eggs*

(2) *Sterile Ringer's Solution* This is prepared according to the following formula

Sodium chloride	*(NaCl)*	*8 0 gm*
Potassium chloride	(KCl)	0 2 gm
Calcium chloride	($CaCl_2$)	0 2 gm
Magnesium chloride	($MgCl_2$)	0 1 gm
Monosodium phosphate	(NaH_2PO_4)	0 1 gm
Sodium bicarbonate	*($NaHCO_3$)*	*0 4 gm*
Distilled water	(H_2O)	1000 ml

It is then autoclaved at 15 pounds pressure for 20 minutes and allowed to cool

(3) *Modified Sterile Ringer's Solution* Prepared by adding 0 25 gram of Loeffler's Dehydrated Blood Serum* to 1000 ml of Ringer's solution which should be made up in addition to the Ringer's solution of (2) Boil serum and Ringer's solution for 1 hour to facilitate solution of serum, filter and autoclave for 20 minutes at 15 pounds pressure

(4) *Sterile Rice Flour* The rice flour is sterilized by placing about 5 grams in a test tube and plugging it with cotton It is distributed evenly and loosely over inner surface of tube by shaking and then sterilized in horizontal position in dry heat at about 90° C for 12 hours, using intermittent sterilization and allowing 4 hours for each period, flour remains white if not overheated

b. Procedure. Wash four eggs thoroughly, rinse, and brush well with 70 per cent ethyl alcohol Break into sterile Erlenmeyer flask containing glass beads and 50 ml of Ringer's solution Emulsify completely by shaking Place about 4 ml of this material in each test tube and sterilize as follows (using autoclave as inspissator) Place tubes in a preheated autoclave in such a position as to produce a slant of about 1 to 1 5 inches close the door and vacuum exhaust valve, *turn on the* steam and open the outside exhaust valve When steam appears from this valve, close it and allow the pressure to rise to 15 pounds then shut off steam and allow pressure to decline to zero remove media from *autoclave Repeat on three successive days, storing* media at room temperature between sterilization

To these sterile solid slants add enough modified Ringer's solution

[illegible] sterile human serum or sterile
h case the mod fied
igers solution *This*
bated at 37 5° C to

(about 5 or 6 ml) to cover egg slant completely Incubate at 37 5° C for 24 hours to determine sterility before adding the sterile rice flour Flour is added by taking up 0.25 ml into a clean sterile dry, wide bore 1 ml pipette and discharging it into the liquid medium by tapping the pipette against the inside wall of the tube The tubes are again incubated at 37.5° C for 24 hours to test for sterility

3 Cleveland and Collier's Medium for Cultivation of Amebae

a Materials.

Bacto-Entamoeba medium
Horse serum
NaCl

b Procedure (1) Suspend 33 grams of the Bacto Entamoeba medium in 1000 ml distilled H_2O and heat to boiling to dissolve completely

(2) Place in tubes and autoclave at 15 pounds pressure (120° C) for 20 minutes

(3) Slant tubes Test for sterility at 37 5° C Overlay slants with sterile horse serum–saline solution (1 6 dilution) Add a 5 mm loop of sterile rice flour

4 Egg Yolk Medium for the Cultivation of Amebae (after Balamuth)

a Materials.

Dehydrated or fresh egg yolk
Liver extract (Lilly No 408)
D basic potassium phosphate (K_2HPO_4)
Potassium acid phosphate (KH_2PO_4)
Sodium chloride
Rice flour

b Procedure. (1) Mix 36 grams of dehydrated egg yolk or the crumbled yolks of 4 hard boiled eggs with 36 ml of distilled water

(2) Add 125 ml of 0 8 per cent NaCl and mix with a rotary beater or Waring Blendor

(3) Heat the mixture over boiling water for 20 minutes after the temperature has reached 80° C and add distilled water to offset the loss by evaporation

(4) Filter The mixture of the dehydrated yolks is difficult to separate through a Buchner funnel but may be passed through a double [illegible]

NaCl

(6) Autoclave at 15 pounds (120° C) for 20 minutes

(7) Cool to below 10° C and filter through a Buchner funnel

(8) Add to the filtrate an equal amount of M/15 potassium buffer adjusted to pH 7 5 prepared by diluting 1 15 a solution of M/1 dibasic potassium phosphate 4 3 parts and M/1 potassium acid phosphate 0 7 parts

(9) Add a 5 per cent crude liver extract (Lilly, No 408) to give a final concentration of 0 5 per cent in order to insure rapid growth

(10) Autoclave and then refrigerate until dispensed in tubes containing 7 to 10 ml

(11) Prior to inoculation add a 5 mm loop of sterile rice flour

5 Alcoholic Extract Medium for the Cultivation of Amebae (after Nelson)

a Materials

Finely divided tissue or egg yolk
95% Ethyl alcohol
Agar
Sodium chloride
Rice flour

This medium is recommended because of its simplicity and because it does not grow *Blastocystis hominis* or a heavy bacterial population

b Procedure. (1) Extract one part of finely divided tissue (such as liver) or egg yolk with 9 parts of 95 per cent ethyl alcohol for 48 hours

(2) Evaporate the alcohol from the stock extract in a boiling water bath and add twice the volume of 2 per cent agar in buffered 0 5 per cent sodium chloride solution (*pH* 7 4)

(3) Tube autoclave and slant

(4) Cover the slants with buffered 0 5 per cent sodium chloride solution The addition of 0 025 per cent of agar to the overlay is beneficial

(5) Sterile rice flour is added at the time of inoculation

6 NNN (Novy, MacNeal and Nicolle's) Medium for Leishmanias

a. Materials

Bacto Agar	14 gm
Sodium chloride	6 gm
Distilled water	900 ml
Sodium hydroxide solution	N/1
Rabbit (or guinea pig) defibrinated blood	10 ml

b Procedure. To a flask containing 900 ml of distilled water add 14 grams of Bacto Agar and 6 grams of sodium chloride Bring to a boil and then neutralize with N/1 NaOH Place 150 ml of the medium in 6 Erlenmeyer flasks and sterilize in autoclave for one-half hour at 12 pounds pressure Store in refrigerator Stock medium will keep for several months if stored at ice box temperatures

Place one of the flasks containing 150 ml of stock medium in a boiling water bath and when agar has melted cool medium to 50° to 55° C and, using sterile technique add 10 ml of defibrinated rabbit blood mixing thoroughly Pipette 5 ml of this medium into test tubes and slant tubes so as to produce a long slant When slants have hardened paraffin the cotton plugs and place in refrigerator for 12 hours subsequently incubating tubes at 37 5° for 24 hours to test for sterility

Antibiotics (penicillin 20 units/ml streptomycin 40 units/ml) are

usually introduced on inoculation of cultures to prevent bacterial over growth of the leishmanias

7 *Diphasic Blood Agar Medium for Trypanosomes and Leishmanias* (NIH Method)

a Materials.

Bacto-Beef (Difco)	25.0 gm
Neopeptone (Difco)	10.0 gm
Bacto-Agar (Difco)	10.0 gm
Sodium chloride	2.5 gm
Distilled water	500 ml

b Procedure. (1) Infuse Bacto Beef and distilled water in water bath for 1 hour, heat mixture for 5 minutes at 80° C to coagulate a portion of the protein

(2) Filter, using ordinary grade of filter paper

(3) Add Neopeptone Bacto Agar and sodium chloride

(4) Adjust the pH to 7.2–7.4 with NaOH

(5) Autoclave at 15 pounds 120° C for 20 minutes

(6) Cool until mixture may be held comfortably in the hand and add 10 per cent defibrinated rabbit blood (For *Trypanosoma lewisi* add 30 per cent defibrinated rabbit blood)

(7) Dispense 5 ml per test tube slant and cool

(8) Before inoculating overlay the slants with 2 ml of sterile Locke's solution prepared by the following formula

Sodium chloride	8.0 gm
Potassium chloride	0.2 gm
Calcium chloride	0.2 gm
Potassium phosphate (monobasic)	0.3 gm
Dextrose	2.5 gm
Distilled water	1000 ml

8 *C.P.L.M (Cysteine-Peptone-Liver Maltose) Medium for the Cultivation of Trichomonas vaginalis (after Johnson and Trussell)*

a Materials

Bacto-Peptone	32.0 gm
Bacto-Agar	1.6 gm
Cysteine HCl	2.4 gm
Maltose	1.6 gm
Liver infusion (Difco)	320 ml
Ringer's solution (NaCl 0.6%, $NaHCO_3$, KCl and CaCl 0.01% each)	960 ml
Sodium hydroxide N/1	11–13 ml

b Procedure (1) Heat the mixture in a boiling water bath to melt the agar and filter through coarse filter paper

(2) Add 0.7 ml of 0.5 per cent aqueous methylene blue Adjust the pH to 5.8 to 6.0 with N/1 HCl or N/1 NaOH

(3) Tube in 8 ml amounts and autoclave

(4) Cool add 2 ml of sterile human serum

(5) Incubate for sterility for at least 4 days at 37.5° C and store at room temperature until used

9 Barret and Yarbrough s Medium for Balantidium coli

a Materials

Inactivated human serum	1 part
Sodium chloride solution 0 5%	16 parts

Sterilize by filtration and distribute in 8 ml. portions in test tubes

b Procedure (1) Inoculate tubes by adding 0 1 ml of feces containing organisms at bottom of tubes with a pipette

(2) Incubate at 37° C and examine in 24 hours

(3) Make transfers every 24 or 48 hours using media near bottom of tubes Cysts also appear in culture Substitution of Locke s or Ringer s solution without dextrose gives better results than salt solution

10 Harada and Mori Test Tube Cultivation Method for Nematode Larvae

This method is useful for demonstration of larvae of *Ancylostoma duodenale Necator americanus Trichostrongylus orientalis* and *Strongyloides stercoralis* Approximately 0 5 gram of feces is smeared on a narrow sheet of filter paper (3 cm x 16 cm) About 5 cm of space on one end and 1 cm (for handling) on the other end is left unsmeared The filter paper is placed in a test tube 18 cm in height and 2 cm in diameter with the unsmeared end (5 cm) toward the bottom Two to 3 ml of water are introduced into the tube then the opening is covered with a piece of polyethylene sheet which is held in place by a rubber band The tube is kept in an incubator at 24° to 28° C for about 10 days Eggs of hookworm and certain other nematodes hatch on the filter paper develop into infective larvae crawl out of the feces and migrate to the water The tubes are examined under low power magnification for presence of larvae If they are present fluid is removed with a pipette and the larvae are identified under higher magnification Incubation for 8 days at 30° C provides the optimum condition for maximum detection of *Strongyloides* larvae Larvae usually are found much earlier than 8 days

11 Media for Fungi

a Materials

Sabouraud s glucose medium	
Glucose (maltose)	40 0 gm
Peptone	10 0 gm
Agar	20 0 gm
Water	1000 0 ml

Keep in 10 ml quantities in stab tubes Melt and allow to cool to 45 C add 10 ... while ... added

Sabouraud s conservation medium	
Peptone	40 0 gm
Agar	20 0 gm
Water	1000 0 ml
Beef infusion blood agar (pH 7 4 to 7 6)	
Beef infusion broth	1000 0 ml
Peptone	20 0 gm
Sodium chloride	5 0 gm
Agar	20 0 gm

Keep in 100 ml quantities in flasks Melt and allow to cool to 45° C add 5 ml. of sterile blood, mix and pour into tubes for slants or sterile petri dishes for plates Test for sterility by incubating at 37.5° C for 24 hours

Penicillin and streptomycin also may be added to this medium

Littman's Oxgall Agar (Difco) is a useful medium for use in the tropics where saprophytic fungi tend to overgrow cultures

Maintain cultures at room temperature for 2 or 3 weeks Transfers of growth from any bit of inoculum are made to fresh tubes for pure cultures Cultures which cannot be readily identified should be maintained on Sabouraud's conservation medium to prevent degenerative loss of diagnostic morphologic characters

b. Procedures Yeastlike cultures are best examined by placing a bit of the culture on a slide in drop of water and adding coverslip to the preparation Filamentous cultures should be examined in a mounting medium These cultures are examined by picking small fragments of the aerial growth from the agar surface by means of a straight inoculating wire bent slightly at the end Place material on slide in a drop of lactophenol cotton blue (see page 803) tease or spread out gently with dissecting needles and add coverglass Gentle heating of such a preparation will drive out air bubbles and allow greater penetration of the stain

12 *Fletcher's Medium for Leptospira (after TM 8–227)*

a Materials.

12% Sterile rabbit serum in sterile distilled water	100 ml
2% Nutrient agar	7 5 ml

b Procedure. (1) Heat rabbit serum solution to 50° C

(2) Add melted nutrient agar

(3) Tube in 5 ml quantities and sterilize by heating at 56° C for 1 hour on 2 successive days

(4) Incubate for sterility

(5) Inoculate with 0 03 ml of blood and incubate at 30° C

(6) Examine for leptospira on a darkfield microscope on the 7th 14th 21st and 28th day Then discard

13 *Sanders' Booster Broth for Screening Enteric Pathogens*

a Materials

Tryptone	20 0 gm
Dibasic sodium phosphate	1 0 gm
Sodium chloride	5 0 gm
Bromcresol purple	0 008 gm
Water distilled	1000 ml

b Procedure

(1) Autoclave the basic broth medium at 15 lb pressure for 15 minutes Allow to cool

(2) Add aseptically

Lactose	10 gm
Sucrose	10 gm
Adjust pH to 7 1±	

(3) Dispense 2 ml aliquots into 13 x 100 mm test tube and store in 4 C refrigerator until use

14 Sanders' Phenol Red Agar Base Medium for Paper Disc Petri Dish Culture Method

a. Materials.

Tryptone	10 0	gm
Sodium chloride	5 0	gm
Sodium thiosulfate	0 6	gm
Ferrous ammonium sulfate	0 4	gm
Phenol red	0 018	gm
Agar	15 0	gm
Water distilled	1000	ml

b. Procedure.

(1) Sterilize in autoclave under 15 lb pressure for 15 minutes
(2) Adjust final pH to 7 4±

15 Tissue and Cell Culture Methods for the Isolation Cultivation and Identification of Viruses and for the Assay of Viral Antibodies

a Cell or tissue culture methods are usually faster and more convenient and accurate than animal inoculation methods for the cultivation and identification of viruses Different technical methods are now used in different laboratories, and a standard procedure has not yet evolved In addition, procedures will vary depending upon the suspected viral agent

b Use of mammalian cell cultures for virus studies was begun with cultures in the form of outgrowths from explanted tissue fragments This simplest method of culture may still be employed for pilot studies of new systems to determine what particular tissue or cells support virus replication Commonly, the virus diagnostic laboratory uses trypsin dispersed renal tissue (from a variety of animals), human amnion cells or one or more of the established cell lines, such as HeLa Infected cell cultures are microscopically examined for specific cytopathic effects of virus as evidenced by cellular destruction or formation of inclusion bodies The type of cellular changes is sometimes suggestive of a particular group of viruses For identification of the virus the neutralization of the specific cytopathogenic effect by known antiserum is used Infected cells may also be identified by use of specific antiviral antibody coupled with fluorescein

c Cell cultures can also be used to assay antibody The same basic principle which underlies any virus neutralization test is employed namely, that antibody will specifically neutralize the infectivity of virus In this case, serial dilutions of serum are added to replicate cell cultures A standard amount of virus is added to the tubes After sufficient time has elapsed to permit destruction of cells in control tubes, the titer of antibody is determined by noting the highest dilution of the serum which prevents destruction of cells Metabolic inhibition tests may also be employed to assay for antibody For example, the pH color test utilizes the fact that, with continued cellular growth in the presence of an im

mune serum virus mixture acidic products of metabolism lower the pH of the medium This effect is readily observed by incorporating a pH indicator such as phenol red in the medium Conversely cell death induced by virus leaves the medium and pH indicator unchanged

VIII Serologic and Immunologic Methods

1 Methods of Collecting Materials for Laboratory Diagnosis of Neurotropic Virus Diseases

a Blood for Complement Fixation and Neutralization Tests. (1) As soon as possible after the onset of illness then again after approximately 3 and 6 weeks collect 20 ml blood samples using sterile precautions

(2) Whole blood may be shipped except in areas where sustained temperatures over 100° F prevail However serum is preferable

(3) In the latter case separate serum from blood using aseptic technique

(4) Blood is shipped in 30 ml vacuum tubes if collected in them blood or serum in sterile Wassermann tubes with sterile rubber or cork stoppers sealed with adhesive

CAUTION The specimen should not be frozen unless serum is submitted

b Specimens for Isolation of the Virus *Blood* (1) Withdraw 12 ml of blood in dry sterile syringe and distribute equally in 3 sterile Pyrex Wassermann tubes Stopper tubes with sterile corks and seal with adhesive tape or fire seal if equipment is available

(2) Freeze contents by immersing tubes in a mixture of alcohol and dry ice Rotate tubes while freezing this distributes the contents over a greater surface area and prevents breakage from expansion of fluid Wrap the tube or tubes in cotton and pack carefully in a vacuum bottle Fill remainder of vacuum bottle with small pieces of dry ice (Dry ice may be broken up by wrapping it in a piece of cloth and then crushing with a hammer)

CAUTION Do not touch dry ice with fingers Use a forceps or spoon to fill bottle Cut a small V shaped slot longitudinally in vacuum bottle cork or place a large bore venipuncture needle through center of cork to allow escape of gaseous CO A tiny hole should also be punched in the outer metal cap of bottle

(3) Stopper bottle and pack carefully

Spinal fluid About 3 ml of spinal fluid should be placed in each of 3 sterile Pyrex Wassermann tubes Stopper, freeze and label as directed for blood

Brain and Cord (1) As soon as possible after death remove brain with sterile precautions before thorax and abdomen are opened

(2) Take several generous blocks from (I) temporal lobe including hippocampus (II) motor cortex (III) midbrain (IV) thalamus (V) pons and medulla (VI) cerebellum and (VII) cervical spinal cord

(3) Blocks of tissue for virus studies may be shipped frozen in dry ice or unfrozen in sterile 50 per cent buffered glycerin solution (see

below) Freezing is preferable Individual blocks of tissue are placed in separate small wide mouth sterile bottles without added fluid stoppered with sterile corks and sealed with adhesive tape Freeze and pack in vacuum bottle as described for blood

If shipment cannot reach the laboratory within 24 to 36 hours the tissues should be shipped in buffered 50 per cent glycerin in a sterile stoppered container

c Preparation of Sterile Buffered Glycerin (1) Citric acid 21 grams in 1000 ml double distilled water

(2) Anhydrous Na_2HPO_4 28 4 grams to 1000 ml double distilled water

(3) Take 9 15 ml of (1) and 90 85 ml of (2) to make 100 ml of buffered solution pH 7 4

(4) Mix equal parts of (3) and C P glycerin fill specimen bottles half full stopper with corks and sterilize at 15 lb steam pressure for 30 minutes

2 Methods of Collecting Material for Laboratory Diagnosis of Rickettsial Infections

Excised tissue blocks (such as brain or testis) and blood specimens are frozen and packed as described above for suspected virus infections

3 The Weil Felix Reaction

Theoretical Considerations The Weil Felix reaction is based on the agglutination of the "O" variant of certain strains of *Proteus X* These strains appear in two growth phases designated as "H" (Ger *Haut*) and "O (Ger *ohne Haut*) The H motile flagellar form spreads rapidly over the surface of the medium the O or nonmotile variant of the organism is used for the agglutination reaction since it is this antigen which reacts specifically" with sera from certain typhus like rickettsial diseases The H or motile variants will be agglutinated by many normal sera

The three type strains of *Proteus X* in general use are X2 X19 and XK

The first two were isolated from the urine of patients ill with classic typhus They originally appeared in the O phase The origin of XK is not entirely clear and was received by Dr Kingsbury in Malaya from the National Type Cultures in London (the K denoting the so called Kingsbury strain) An additional strain XL isolated by Dr Lima in an endemic center of "exanthematic typhus" at *Sao Paulo Brazil is also* frequently used According to Felix this strain is of the X19 type but also produces agglutinins for XK, which is not true of the original X19 strain.

X19 is of the greatest diagnostic importance in louse borne and flea borne typhus

as well
ain and
than for

OX19

Strains of *Proteus* X have also been recovered from the brain bone marrow, spleen liver, kidney bile and heart blood The organism is considered by Felix as the cultivable saprophytic stage of the specific infecting agent

Cultivation of Proteus X Strains The strains should be carried on fresh meat infusion agar adjusted to pH 6 8 All strains are in some degree unstable i e there is a tendency to an O—OH (nonmotile to motile) reversion This is most marked in the XK strain and least in the X2 Excess moisture hastens the reversion Consequently it is of greatest importance that all O variants be carried on a medium from which excess moisture has been removed by drying in the incubator for several days To assure H variants on the other hand it is just as important that the medium has its full moisture content Although media made from dehydrated preparations support a fairly heavy growth cultures carried on such media may show a decreased agglutinability

The Test. In the usual macroscopic tube test 0 5 ml of serial serum dilutions 1 10 1 20 etc are placed in a series of agglutination tubes and 0 5 ml of a 24 hour suspension of organisms killed by alcohol phenol formalin or by heat and standardized to MacFarland nephelometer reading No 3 or to a "500" silica standard are added to each tube thereby doubling the dilutions The rack is shaken gently placed at 37° C for 2 hours and stored in the ice box for 48 hours Twenty four hours at ice box temperature gives only a slightly lower reading Usual

and is massed at the bottom of the tube

Interpretation. Normal sera may show a low agglutinin titer for OXK or *OX19* seldom for OX2 *If 2* or more successive serum samples are available a sharp rise in titer is of definite significance As a rule serum taken during the first week will not show a titer higher than 1 80 or 1 160 This titer will then serve as a basis for later tests When possible second and third samples should be tested the second taken on or about the tenth day and the third at the end of the second or during the third week of the disease or during early convalescence

It must be remembered that as in any serologic test the Weil Felix reaction is only an aid to diagnosis It is only a part of the picture and should be interpreted as such An occasional serum may show a relatively high titer in the absence of any apparent rickettsial infection (see pages 61–106)

Sera of infected guinea pigs do not give a Weil Felix reaction

4 *Hemagglutination Inhibition Test for the Diagnosis of Virus Influenza* (after the WRAIR)

The basis for the hemagglutination inhibition test is the fact that certain viruses possess the capacity to agglutinate certain red blood cells and that specific antibody prevents this hemagglutination This reaction therefore can be utilized for identification of a virus or for antibody assay

a. Materials.

Physiologic saline made with freshly boiled distilled water
Standard 0 5% suspension type 'O human red cells (or chicken red cells) fresh or preserved in dextrose (2 05%) sodium citrate (0 80%) and so

b. Preparation of Material for Influenza A, A1, A2 and B. (1) Rehydrate the antigens with sterile distilled water as directed on the label Rehydrated antigens are stable for a period of months at −20° C and for at least 3 weeks at 4° C

(2) Titrate the antigens to determine the hemagglutinating unit of each The unit is 0 5 ml of the highest dilution of antigen which completely agglutinates 0 5 ml of standard human erythrocyte suspension in 1¼ hours

(3) Each antigen for use in the test is to contain 4 units in 0 25 ml This is ⅛ the highest dilution of antigen which showed complete agglutination in the antigen titration

c. Procedure for Influenza A, A1, A2 and B. (1) 0 3 ml amounts of each serum to be tested are inactivated at 56° C for 30 minutes

(2) Dilute each serum 1 8 by adding 2 1 ml physiologic saline

(3) Set up identical series of twofold serial dilutions of each serum for each antigen such that each tube contains 0 25 ml and the serum dilutions range from 1 8 to 1 4096

(4) Add 0 25 ml of test antigen to each tube of a series

(5) Shake well

(6) Add 0 5 ml of the standard erythrocyte suspension to each tube

(7) Shake well and incubate at 22 to 25° C for 60 minutes without disturbing the racks The tests are read and recorded in terms of degree of inhibition of agglutination by each serum using each antigen The titer of a given serum using a given antigen is defined as the highest dilution of serum which effects complete inhibition of agglutination

(8) *Controls* (*a*) Antisera from roosters immunized against the viruses used in the test are used for control purposes The tests with positive control sera serve (1) to confirm the identity of the antigen used, and (2) to test further the specificity and quantity of the reacting materials in the test antigens

(*b*) The test antigens must be retitrated at the same time that the hemagglutination inhibition tests are performed The initial dilution is however, the dilution of the test antigen These retitrations are read ... the first

elutes from red blood cells at room temperature, all tests with the C agent are performed with chilled reagents and incubation is carried out in the refrigerator (4 to 6° C) for 80 to 90 minutes With these exceptions, the procedures as outlined in section c are followed

e Interpretation. Results are reported in terms of the titers of each of the paired sera obtained with each antigen A fourfold or greater increase in titer during convalescence is considered of diagnostic significance Influenza vaccination histories should be ascertained A rise in titer to both type A and type B virus should be suspected of being due to recent vaccination and a thorough check should be made Concurrent infection in a single individual with both type A and type B influenza virus is a rare occurrence

Individual diagnoses on a representative group of individuals are usually sufficient to detect the existence of an epidemic of influenza

5 Methods of Collecting Material for Laboratory Diagnosis of Spirochetal Infections

Blood *Spirillum minus* of rat bite fever does not live long after blood has been drawn, so animal inoculations have to be made almost immediately The relapsing fever spirochetes and *Leptospira ictero haemorrhagiae* however remain viable for a long time in sterile drawn blood so that samples of whole blood for animal inoculation may be taken at the height of the febrile reaction and shipped in 30 ml vacuum collecting tubes or in sterile Wassermann tubes as described above for blood for complement fixation and neutralization tests in neurotropic viruses Refrigeration but not freezing of the blood samples is recommended When the samples reach the laboratory grind clot in a mortar under sterile conditions in physiologic salt solution and inoculate into mice or other experimental animals

Cerebrospinal Fluid In cases of relapsing fever and *Leptospira icterohaemorrhagiae* infection showing meningeal symptoms the cerebrospinal fluid may contain spirochetes Like blood it is collected aseptically and shipped in sterile tubes to the laboratory where it is centrifuged for a half hour at 2000 r p m and the sediment examined in the dark field for spirochetes

6 The Complement Fixation Test for Leptospirosis (after the WRAIR)

Introduction The complement fixation test for leptospirosis employs the standard Kolmer technique utilizing some vibrated leptospiral antigens Since these antigens have broad spectrums and antibodies are produced by the various species of leptospirae they will cross in the test It is recommended that sera be tested against a battery of three antigens *L icterohaemorrhagiae L hyos* and *L grippotyphosa* This combination of antigens has been found to detect antibodies against all species of leptospirae which have been tested

Preparation of Sera Inactivate cell free serum (0 75 ml) in water bath (56° C for 30 minutes)

Reagents (1) An 0 85 per cent sodium chloride solution containing 0 1 gram *magnesium sulfate per liter (Kolmer saline)*

(2) A 2 0 per cent sheep cell suspension

(3) *Antigens* *L icterohaemorrhagiae L hyos* and *L grippotyphosa* antigens should be rehydrated according to the procedure recommended by the manufacturer

a. Materials.

Pl [illegible]
S

b. Preparaton of Material for Influenza A, A1, A2 and B. (1) Rehydrate the antigens with sterile distilled water as directed on the label Rehydrated antigens are stable for a period of months at −20° C and for at least 3 weeks at 4° C

(2) Titrate the antigens to determine the hemagglutinating unit of each The unit is 0 5 ml of the highest dilution of antigen which completely agglutinates 0 5 ml of standard human erythrocyte suspension in 1¼ hours

(3) Each antigen for use in the test is to contain 4 units in 0 25 ml This is ⅛ the highest dilution of antigen which showed complete agglutination in the antigen titration

c. Procedure for Influenza A, A1, A2 and B. (1) 0 3 ml amounts of each serum to be tested are inactivated at 56° C for 30 minutes

(2) Dilute each serum 1 8 by adding 2 1 ml physiologic saline

(3) Set up identical series of twofold serial dilutions of each serum for each antigen such that each tube contains 0 25 ml and the serum dilutions range from 1 8 to 1 4096

(4) Add 0 25 ml of test antigen to each tube of a series

(5) Shake well

(6) Add 0 5 ml of the standard erythrocyte suspension to each tube

(7) Shake well and incubate at 22 to 25° C for 60 minutes without disturbing the racks The tests are read and recorded in terms of degree of inhibition of agglutination by each serum using each antigen The titer of a given serum using a given antigen is defined as the highest dilution of serum which effects complete inhibition of agglutination

(8) *Controls* (*a*) Antisera from roosters immunized against the viruses used in the test are used for control purposes The tests with positive control sera serve (1) to confirm the identity of the antigen used, and (2) to test further the specificity and quantity of the reacting materials in the test antigens

(*b*) The test antigens must be retitrated at the same time that the hemagglutination inhibition tests are performed The initial dilution is however, the dilution of the test antigen These retitrations are read after 65 to 75 minutes Complete agglutination should occur in the first four tubes of each antigen tested and there should be less than complete agglutination in the fifth and remaining tubes

d. Procedure for Influenza C. Since influenza C virus rapidly elutes from red blood cells at room temperature, all tests with the C agent are performed with chilled reagents and incubation is carried out in the refrigerator (4 to 6° C) for 80 to 90 minutes With these exceptions, the procedures as outlined in section *c* are followed

e. Interpretation. Results are reported in terms of the titers of each of the paired sera obtained with each antigen A fourfold or greater increase in titer during convalescence is considered of diagnostic significance Influenza vaccination histories should be ascertained A rise in titer to both type A and type B virus should be suspected of being due to recent vaccination, and a thorough check should be made Concurrent infection in a single individual with both type A and type B influenza virus is a rare occurrence

Individual diagnoses on a representative group of individuals are usually sufficient to detect the existence of an epidemic of influenza

5 *Methods of Collecting Material for Laboratory Diagnosis of Spirochetal Infections*

Blood. *Spirillum minus* of rat bite fever does not live long after blood has been drawn, so animal inoculations have to be made almost immediately The relapsing fever spirochetes and *Leptospira icterohaemorrhagiae*, however, remain viable for a long time in sterile drawn blood so that samples of whole blood for animal inoculation may be taken at the height of the febrile reaction and shipped in 30 ml vacuum collecting tubes or in sterile Wassermann tubes as described above for blood for complement fixation and neutralization tests in neurotropic viruses Refrigeration, but not freezing of the blood samples is recommended When the samples reach the laboratory, grind clot in a mortar under sterile conditions in physiologic salt solution and inoculate into mice or other experimental animals

Cerebrospinal Fluid. In cases of relapsing fever and *Leptospira icterohaemorrhagiae* infection showing meningeal symptoms the cerebrospinal fluid may contain spirochetes Like blood it is collected aseptically and shipped in sterile tubes to the laboratory where it is centrifuged for a half hour at 2000 r p m and the sediment examined in the dark field for spirochetes

6 *The Complement Fixation Test for Leptospirosis* (after the WRAIR)

Introduction. The complement fixation test for leptospirosis employs the standard Ko'
antigens Since these
produced by the vari
test It is recommended that sera be tested against a battery of three antigens, *L icterohaemorrhagiae*, *L hyos* and *L grippotyphosa* This combination of antigens has been found to detect antibodies against all species of leptospirae which have been tested

Preparation of Sera. Inactivate cell free serum (0 75 ml) in water bath (56° C for 30 minutes)

Reagents. (1) An 0 85 per cent sodium chloride solution containing 0 1 gram magnesium sulfate per liter (Kolmer saline)

(2) A 2 0 per cent sheep cell suspension

(3) *Antigens* *L icterohaemorrhagiae*, *L hyos* and *L grippotyphosa* antigens should be rehydrated according to the procedure recommended by the manufacturer

(4) Stock dilution of 1 100 hemolysin

(5) *Complement* Rehydrate lyophilized complement by dissolving in the prescribed amount of buffered diluent supplied with it and store under refrigeration at all times

Titration of Hemolysin Hemolysin is titrated according to standard Kolmer technique The unit is read as the highest dilution of hemolysin that gives complete hemolysis Two units contained in *0 5 ml* are used in the complement titration and in the test

Titration of Complement Complement is titrated according to standard Kolmer technique The smallest amount of complement giving complete hemolysis is the exact unit The next larger amount (0 05 more) is the full unit Use 2 *full units* contained in 1 0 ml in the test

Complement Fixation Test for Leptospirosis (1) The tests are *conducted in ¼ volume by reducing the amounts of reagents and sera by* half The hemolysin and complement however are titrated at full volume as described for the regular test The table (below) should be followed in performing the test

(2) Controls of positive and negative sera for each antigen should be included

(3) After addition of hemolysin and corpuscles mix contents of each *tube by thorough shaking of the rack and place in the water bath at 37°* C for 10 minutes longer than the time required for the antigen controls to clear

TUBE NO	KOLMER SALINE *SOLUTION*	ANTIGEN *L ictero*	*L grippo*	*L hyos*	COMPLEMENT (2 FULL *UNITS*)		HEMOLYSIN 2 UNITS	CORPUSCLES 2%
Patient's Serum	ml	ml	ml	ml	ml		ml	ml
1 0 1 ml	None	0 25	None	None	None	Refrigerate at 6° to 8° C for 15 to 18 hours then place in 37° C water bath for 10 minutes	0 25	0 25
2 0 1 ml	None	None	0 25	None	0 5		0 25	0 25
3 0 1 ml	None	None	None	0 25	0 5		0 25	0 25
4 0 1 ml	0 25	None	None	None	0 5		0 25	0 25
Controls								
5 *L ictero* antigen	0 25	0 25	None	None	0 5		0 25	0 25
6 *L grippo* antigen	0 25	None	0 25	None	0 5		0 25	0 25
7 *L hyos* antigen	0 25	None	None	0 25	0 5		0 25	0 25
8 Hemolytic system	0 5	None	None	None	0 5		0 25	0 25
9 Corpuscle	1 25	None	None	None	None		None	0 25

(4) Read as negative 1 2 3 or 4 plus according to standard methods of reading of complement fixation tests

(5) The above procedure is a screening test and all sera showing 2 plus or greater fixation of complement must be titrated to determine the exact titer

Interpretation. Leptospiral complement fixing antibodies are usually demonstrable by the 8th day of the disease and may appear as early as the 4th The maximum titer (in the order of 1 128–1 512) is usually attained during the second week of illness Complement fixing antibodies remain in detectable levels for periods varying from 3 to over 12 months For this reason demonstration of a rise in titer is essential to the confirmation of the clinical diagnosis of acute leptospirosis Since it is impossible to determine the infecting strain by the examination of sera with antigens of this type positive results should be reported as "Complement fixation test for leptospirosis positive (indicate titer) or negative"

7 Dye Test or Cytoplasm Modifying Test for Toxoplasmosis (after Sabin and Feldman)

a Reagents (1) *Toxoplasma* The strain used should multiply extensively in the peritoneal cavity of mice in 3 to 4 days

(2) *Accessory Factor* Human serum which in the fresh state can be incubated with *Toxoplasma* at 37° C for 1 hour without affecting the staining of the cytoplasm by methylene blue at pH 11 this may be stored for at least 4 years in dry ice

(3) *Positive Control Serum* Any human or animal serum that has been found to have cytoplasm modifying antibodies

(4) *Methylene Blue at pH 11* Prepared daily by mixing 3 ml saturated alcoholic solution of methylene blue with 10 ml of buffer at pH 11 (9 73 ml of 0 53 per cent sodium carbonate plus 0 27 ml of 1 91 per cent sodium borate [$Na_2B_4O_7 \cdot 10H_2O$]) Commercially available buffer tablets (pH 10 8) can be used to make the buffer solution

(5) *Anticoagulant* A 1 per cent solution of heparin in 0 9 per cent solution of sodium chloride

b Procedure (1) Each serum should be screened by testing the 1 16 1 64 and 1 256 dilutions Fourfold dilutions of the test serums in 0 1 ml amounts prepared in 0 9 per cent solution of sodium chloride should be ready before the *Toxoplasma* suspension is prepared

(2) The *Toxoplasma* suspension for use in the test is prepared by mixing 0 2 ml of undiluted peritoneal exudate with 0 02 ml of 1 per cent heparin and 0 8 ml of the normal human serum containing the accessory factor This mixture should be put in a refrigerator immediately after preparation but the whole test should be set up within 1 hour after peritoneal exudate is removed from the animal

(3) A preliminary examination of the condition of the *Toxoplasma* organisms is made by adding 0 1 ml of this mixture to 0 1 ml of 0 9 per cent solution of sodium chloride incubating at 37° C for 20 minutes and examining with the dye to make certain that the cytoplasm of at

least 90 per cent of the extracellular *Toxoplasma* organisms are well stained

(4) 0 1 ml of the *Toxoplasma accessory factor mixture is added to* 0 1 ml of the various serum dilutions in small tubes

(5) After incubation for 1 hour at 37° C in a water bath, 0 02 ml of the methylene blue is added to each tube

(6) One drop from each tube is put on a slide, covered with a coverslip and examined with the high power lens of a microscope

(7) The number of extracellular *Toxoplasma* organisms with stained or unstained cytoplasm *is determined* The highest dilution of serum in which 50 per cent or more of the organisms have unstained cytoplasm is the titer Ordinarily the cytoplasm modifying antibody develops within 10 to 20 days Titers of 1 256 to 1 4000 or higher can persist for at least 5 years

8 Fluorescent Stain for Toxoplasma in Exudates (after Goldman)

a. Materials.

1 Preparation of fluorescent antibody

One volume of human serum having a titer of at least 1 4000 in the methylene blue test (see p 833) is treated with an equal volume of *saturated ammonium sulfate to precipitate the globulin fraction* After about 30 minutes, the precipitate is centrifuged down and the supernate discarded The sediment is dissolved in 1 volume of distilled water, and dialyzed against saline The protein concentration is then determined by any standard method

The following reagents are combined in an Erlenmeyer *flask fitted* with a mechanical stirrer 10 ml saline, 3 ml carbonate bicarbonate buffer (0 5 *M*, *p*H 9 0), 2 ml acetone The mixture is cooled in an acetone dry ice bath until crystals of ice form To this cooled mixture is added, with stirring, 10 ml of the diluted globulin fraction of known concentration The mixture is again cooled in the cold bath until crystals of ice form, and to this cooled, stirred solution is added slowly 1 5 ml *of acetone containing the required amount of fluorescin isothiocyanate* (0 5 mgm of dye per mgm of protein) After addition of the solution of the dye in acetone, the mixture is transferred to the cold room and stirring is continued for 18 hours The mixture is then dialyzed against phosphate buffered saline 01 *M*, *p*H 7 2) until dialysate shows no fluorescence when viewed with a *small portable ultraviolet light* The conjugated globulin is precipitated several times with half saturated ammonium sulfate, as described above, to remove uncombined fluorescein and the final product is dialyzed against phosphate buffered saline and stored at −20° C until ready for use

Staining Procedure Smears are prepared *from blood, bone marrow*, spinal fluid or exudates by allowing small drops to dry on slides over an area about 5 mm in diameter [illegible] ars are dry, they are stained immediately and stored at −20° C [illegible] ml of labeled antibody is placed on [illegible] ear which is [illegible] a wet chamber at 37° C After 1 ho[illegible] is removed [illegible] d *in saline for 10*

minutes and tap water for 5 minutes After drying a drop of alkaline buffered glycerin (9 parts of glycerin and 1 part of 0 15 *M* phosphate buffer, pH 8 0) is added, and a coverslip applied

Fluorescence Microscopy. Ultraviolet light sources are available from several firms A conventional microscope equipped with a dark field condenser is used

A Corning glass filter, No 5850 (8 mm) is used between the ultra violet light source and the microscope, and Corning filters 3486 (2 mm) plus 9780 (5 mm) are used in the eyepieces

Results. *Toxoplasma* organisms, if present appear brightly fluores cent against a dark background The test is highly specific

The underlying principles of this technique of course can be applied to many different organisms, and these new tests are of great diagnostic value

9 Napier's Aldehyde (Formol-Gel) Test for Kala Azar

This is a test for euglobulin, which is increased in kala azar as well as in some other diseases

The test in kala azar is not ordinarily of diagnostic value until after the third to fifth month of the disease, and the reaction may remain positive for about 4 months after recovery

a. Procedure. To 1 ml of clear serum of the patient add 1 or 2 drops full strength commercial formalin

If serum becomes solidified and opaque like boiled egg white within 15 [illegible]

When serum remains clear it is read as a negative even though solidifica tion occurs

10 Precipitin Test to Determine Source of Mosquito Blood Meals

(1) Collect engorged female mosquitoes early in morning Trans port to laboratory in vials kept iced in vacuum jug

(2) Kill mosquito by chloroforming, place it on its back, head pointing away With a small curved tissue forceps take hold of mosquito near anterior end of abdomen and push lower abdomen against a small strip of filter paper of the harder sort (as Whatman No 5), rupturing abdomen wall and stomach in such a manner that blood will be spread and absorbed by paper

(3) Write pertinent data as to date and place of collecting on re mainder of the strip of filter paper

(4) Store strips in dry, cool, insect proof place until tests can be made

(5) Cut off blood spot on filter paper into 2 to 3 ml of physio logic salt solution, and allow to soak for 1 hour at room temperature, shaking from time to time If blood spot is unusually small a smaller amount of saline solution should be used It is not necessary to filter this solution but it should stand a while before the supernatant fluid is drawn off for precipitin test

least 90 per cent of the extracellular *Toxoplasma* organisms are well stained

(4) 0 1 ml of the *Toxoplasma* accessory factor mixture is added to 0 1 ml of the various serum dilutions in small tubes

(5) After incubation for 1 hour at 37° C in a water bath, 0 02 ml of the methylene blue is added to each tube

(6) One drop from each tube is put on a slide, covered with a coverslip and examined with the high power lens of a microscope

(7) The number of extracellular *Toxoplasma* organisms with stained or unstained cytoplasm is determined The highest dilution of serum in which 50 per cent or more of the organisms have unstained cytoplasm is the titer Ordinarily the cytoplasm modifying antibody develops within 10 to 20 days Titers of 1 256 to 1 4000 or higher can persist for at least 5 years

8 *Fluorescent Stain for Toxoplasma in Exudates* (after Goldman)

a. Materials.

1 Preparation of fluorescent antibody.

One volume of human serum having a titer of at least 1 4000 in the methylene blue test (see p 833) is treated with an equal volume of saturated ammonium sulfate to precipitate the globulin fraction After about 30 minutes, the precipitate is centrifuged down and the supernate discarded The sediment is dissolved in 1 volume of distilled water, and dialyzed against saline The protein concentration is then determined by any standard method

The following reagents are combined in an Erlenmeyer flask fitted with a mechanical stirrer 10 ml saline, 3 ml carbonate bicarbonate buffer (0 5 *M*, *pH* 9 0), 2 ml acetone The mixture is cooled in an acetone dry ice bath until crystals of ice form To this cooled mixture is added, with stirring 10 ml of the diluted globulin fraction of known concentration The mixture is again cooled in the cold bath until crystals of ice form, and to this cooled, stirred solution is added slowly 1 5 ml of acetone containing the required amount of fluorescein isothiocyanate (0 5 mgm of dye per mgm of protein) After addition of the solution of the dye in acetone, the mixture is transferred to the cold room and stirring is continued for 18 hours The mixture is then dialyzed against phosphate buffered saline 01 *M*, *p*H 7 2) until dialysate shows no fluorescence when viewed with a small portable ultraviolet light The conjugated globulin is precipitated several times with half saturated ammonium sulfate, as described above, to remove uncombined fluorescein and the final product is dialyzed against phosphate buffered saline and stored at —20° C until ready for use

Staining Procedure. Smears are prepared from blood bone marrow, spinal fluid or exudates by allowing small drops to dry on slides over an area about 5 mm in diameter When smears are dry, they are stained immediately and stored at —20° C Next 04 ml of labeled antibody is placed on a dried smear which is then put in a wet chamber at 37° C After 1 hour, the slide is removed and washed in saline for 10

minutes and tap water for 5 minutes After drying a drop of alkaline buffered glycerin (9 parts of glycerin and 1 part of 0 15 *M* phosphate buffer, pH 8 0) is added and a coverslip applied

Fluorescence Microscopy. Ultraviolet light sources are available from several firms A conventional microscope equipped with a dark field condenser is used

A Corning glass filter, No 5850 (8 mm) is used between the ultra violet light source and the microscope and Corning filters 3486 (2 mm) plus 9780 (5 mm) are used in the eyepieces

Results. *Toxoplasma* organisms if present appear brightly fluores cent against a dark background The test is highly specific

The underlying principles of this technique of course can be applied to many different organisms and these new tests are of great diagnostic value

9 Napier's Aldehyde (Formol-Gel) Test for Kala Azar

This is a test for euglobulin, which is increased in kala azar as well as in some other diseases

The test in kala azar is not ordinarily of diagnostic value until after the third to fifth month of the disease and the reaction may remain positive for about 4 months after recovery

a **Procedure** To 1 ml of clear serum of the patient add 1 or 2 drops full strength commercial formalin

If serum becomes solidified and opaque like boiled egg white within 15 minutes it is read as a strong positive If a similar result is obtained within 24 hours the reaction is still considered positive If serum solidifies without becoming altogether opaque the interpretation is doubtful When serum remains clear it is read as a negative even though solidifica tion occurs

10 Precipitin Test to Determine Source of Mosquito Blood Meals

(1) Collect engorged female mosquitoes early in morning Trans port to laboratory in vials kept iced in vacuum jug

(2) Kill mosquito by chloroforming, place it on its back, head pointing away [illegible]
near anterior er[illegible]
strip of filter pa[illegible]
abdomen wall and stomach in such a manner that blood will be spread and absorbed by paper

(3) Write pertinent data as to date and place of collecting on re mainder of the strip of filter paper

(4) Store strips in dry cool insect proof place until tests can be made

(5) Cut off blood spot on filter paper into 2 to 3 ml of physio logic salt solution, and allow to soak for 1 hour at room temperature, shaking from time to time If blood spot is unusually small a smaller amount of saline solution should be used It is not necessary to filter this solution but it should stand a while before the supernatant fluid is drawn off for precipitin test

(6) A few cubic millimeters of diluted previously prepared anti human serum is carefully pipetted into a small serum tube so as not to wet the sides above the serum level

The dilution of the antihuman serum depends on its known titer If the titer is from 3000 to 4000 a titer rarely attained in the rabbit the serum should be diluted about 1 7 Sera of lower titer are diluted correspondingly

(7) The supernatant fluid from (5) is carefully layered onto the antihuman serum

(8) A cloudiness or opalescence at the interphase of the 2 fluids denotes a positive precipitin test indicating that the mosquito had probably bitten man

(9) If the reaction does not occur immediately, inspect at intervals of 10 minutes for 1 hour

(10) Similar tests can be made with antihorse antipig sera etc

11 Intradermal Test for Trichinosis

a Materials

Stock antigen prepared from lyophilized *Trichinella spiralis* larvae

b Procedure (1) Dilute stock trichina antigen 1 10 000 with physiologic saline and keep refrigerated until use

(2) Inject 0 1 ml of antigen intracutaneously on one forearm and an equal amount of saline control on the other forearm In positive reactions a white swelling surrounded by an unraised irregular erythematous area of about 3 cm in diameter appears at the site of injection The reaction reaches its maximum in 10 minutes and begins to fade in 15 to 20 minutes In negative tests there is no reaction to the antigen

12 Intradermal Test for Echinococcus Infection

a Materials

Stock antigen of purified powdered hydatid fluid

b Procedure (1) Dilute the stock antigen 1 10 000 with physiologic saline

(2) Inject 0 2 ml of antigen intradermally on the upper arm and 0 2 ml of saline control on the other arm In positive cases a wheal develops at the site of injection of antigen within 15 minutes

13 Reference Diagnostic Services in Parasitology to State Health Department Laboratories Performed by the Communicable Disease Center (CDC) of the Public Health Service (Chamblee Georgia)*

Toxoplasmosis

(1) Complement fixation test
(2) Dye test

Trichinosis

(1) Complement fixation test
(2) Bentonite flocculation test

* Specimens of serum must be sent to the local State Health Department Laboratory which will transmit them to the CDC The diagnostic specimens must not be sent to the CDC directly by the physician

Echinococcosis

(1) Complement fixation test
(2) Bentonite flocculation test*
(3) Hemagglutination procedure*

Visceral larva migrans

(1) Bentonite flocculation test*
(2) Hemagglutination procedure*

* *Experimental tests* which will be performed upon request

IX. Miscellaneous

1 Parasite Counts in Malaria (after Wilcox)

a. Procedure There are both thick smear and thin smear methods of enumerating malaria parasites, but the former is recommended even for relatively inexperienced workers

(1) Make a thick smear at the same time the blood is drawn for a white count

(2) Fix and stain the thick film

(3) Count 100 white cells (or multiples of 100) on the thick film

(4) Count the malaria parasites seen in the same microscopic fields with the white cells

(5) Calculate the parasites per cubic millimeter of blood as follows

$$\frac{x \text{ (No of parasites per cu mm)}}{\text{White cell count per cubic mm}} = \frac{\text{No of parasites counted in the same fields with 100 white cells}}{\text{No of white cells counted (100 in this case)}}$$

x = No of parasites/cu mm of blood

Example

$$\frac{x}{4000} = \frac{1200}{100}$$
$$100x = 4\,800\,000$$
$$x = 48\,000$$

2 Examination of Female Anopheline Mosquitoes for Malarial Parasites

It is desirable under certain conditions to know whether mosquitoes contain oocysts on the stomach wall or whether the salivary glands contain sporozoites

a. Procedure. (1) Kill female mosquitoes a few at a time with chloroform carbon tetrachloride or tobacco smoke and identify species It may be desirable to mount identical specimens for subsequent confirmation

(2) Do not dissect recently engorged mosquitoes Remove legs and wings dip quickly into 35 to 50 per cent alcohol and place at edge of drop of physiologic saline with head pointing away

1

partially severed terminal abdominal segments and exert gentle inter

mittent traction to draw out stomach attached malpighian tubules and ovaries

(5) Carefully set aside thorax and head of mosquito in saline for subsequent examination

(6) Sever gut posterior to stomach discarding attached malpighian tubules intestine ovaries and débris transfer to a clean drop and carefully lower coverglass onto stomach

(7) Examine stomach wall for oocysts which may be recognized as follows

(*a*) *Young oocysts* are clear round oval bodies 6 to 12 μ in diameter are more refractile than stomach cells and contain minute pigment granules

(*b*) *Intermediate oocysts* are denser than stomach cells 12 to 40 μ in diameter, and contain clumps of pigment

(*c*) *Mature oocysts* are 30 to 80 μ in diameter show fine striations owing to enormous numbers of attentuated spindle shaped sporozoites 12 to 44 μ in length Pigment granules are not readily visible

CAUTION Protruding unpigmented stomach cells may be confused with immature oocysts of *Plasmodium*

(8) *Salivary Gland Dissection* Place head and thorax (or entire mosquito with wings and legs removed if it is being examined only for sporozoites) in a drop of physiologic saline tinted with methylene blue with body pointing away

(9) Exert gentle pressure on anterior thorax so that neck bulges slightly place second needle behind head and draw away from thorax

(10) Transfer head and attached tissue to a fresh drop of saline and search for blue stained salivary glands under dissecting binocular or hand lens

(11) Tease out one or both trilobed glands and transfer carefully to a fresh drop on same side gently lower coverglass

(12) Examine all 3 lobes of each gland carefully under a high dry lens for the characteristic sporozoites If necessary confirm with oil immersion objective

(13) Crush glands by exerting pressure on cover with clean instrument search again

(14) If glands are positive remove coverglass and allow material on it and slide to dry Fix both in methyl alcohol and stain with Giemsa s or Wright s stain If desired coverglass may be mounted smear side up on slide Examine with high dry and oil immersion objective for sporozoites which appear as slender blue staining spindles with a central red chromatin dot

3 Examination of Mosquitoes for Filarial Worms

In areas where filariasis is endemic it is sometimes desirable to dissect mosquitoes to determine the per cent infected

a **Procedure** (1) Proceed as in (1) and (2) above

(2) Sever head and place in separate drop of saline Carefully dissect thorax teasing all tissues apart add coverglass and examine for developing parasites

(3) Carefully dissect proboscis and head for presence of infective larvae, which are usually 0 1 mm or more in length

4. *Mounting Entomologic Specimens for Study*

fied, as necessary, for other forms

(1) *Use of Potassium Hydroxide* Opaque or heavily chitinized specimens may require preliminary soaking in a 10 per cent solution of potassium hydroxide Such treatment takes from a few minutes to

(*b*) Dehydrate in alcohol as follows

50% alcohol–15 minutes*
70% alcohol–15 minutes
85% alcohol–15 minutes
95% alcohol–15 minutes
absolute alcohol–10 minutes

* *These time intervals are minimum–longer periods in each alcohol may result in better preparations*

(*c*) Clear in xylene for approximately 10 minutes

(*d*) Mount in balsam under a coverglass This technique produces good permanent mounts

If Euparal or Diaphane is used the procedure is the same except that specimens do not require clearing in xylene but may be mounted directly from absolute alcohol

(3) *Mounting in Berlese's Medium* (*a*) FORMULA

Gum arabic	8 gm
Water (distilled)	8 ml
Glycerin	5 ml
Chloral hydrate	70 gm
Glacial acetic acid	3 ml

Dissolve gum arabic in water and add other ingredients in order Strain through muslin before use

(*b*) *Procedure* Specimens may be mounted in Berlese's medium directly from water, or if preserved in alcohol may be mounted after rinsing in water This produces good mounts of a semi permanent nature

b. Maggots. Only the mouth hooks and posterior spiracles of most maggots are dissected off and mounted

c. Ticks. Ticks may be punctured, cleared and mounted as above Live mounts, the specimens being placed between a slide and a strip of adhesive tape, are often more satisfactory Some specimens should be placed in a dorsal position, others in a ventral position, so that all structures may be seen

d. Pinned Specimens Adult specimens of mosquitoes, flies, bees, wasps ants, beetles, bugs and other groups may be mounted on insect

pins in any of several ways Such specimens require no special preservation and if kept in pest proof boxes remain suitable for study for many years The following techniques are recommended

(1) For larger insects (except COLEOPTERA) direct impalement through center of thorax is the most desirable procedure Specimen is pushed up to within ¼ inch of pinhead This allows ample room below for small labels on which are written date and place of collection collector s name and other pertinent data

(2) For beetles procedure is same save that pin passes through base of right elytron (wing cover)

(3) For smaller forms 2 techniques are employed

(*a*) *With small bugs beetles and other species* characterized by fairly rigid chitin and absence of body hair use of small cardboard points is preferred Thrust pin through broader end of point add a small drop of shellac or similar material to fasten extremity of point to right side of insect s thorax

(*b*) With more delicate forms possessing an abundance of hair on wings or body very fine pins termed "minuten nadeln are recommended Minuten which are approximately ¹ inch in length are thrust up through one end of a small bit or cork balsa wood or especially prepared cardboard which in turn is impaled on a standard pin in usual manner Point of minuten is usually thrust up through specimen from below, though some prefer insects be mounted in a lateral position

e Fluid Preservation of Large Specimens Most ticks spiders scorpions centipedes and larger larvae of all types *do not lend them*selves either to pinning or to mounting on slides These are best preserved in vials containing 70 per cent alcohol or 4 per cent formaldehyde For study they may be transferred to a watch glass and examined with a hand lens or binocular microscope

Index

Page numbers in *italics* refer to illustrations and tables